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Chang et al.

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(54) **OPTICAL DETECTION FOR BIO-ENTITIES**

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(51) **Int. Cl.**

C12Q 1/6869	(2018.01)
G01N 27/447	(2006.01)

(Continued)

(52) **U.S. Cl.**
CPC .... ***C12Q 1/6869*** (2013.01); ***B01F 33/3021*** (2022.01); ***B01F 33/3031*** (2022.01); (Continued)

(58) **Field of Classification Search**
None
See application file for complete search history.

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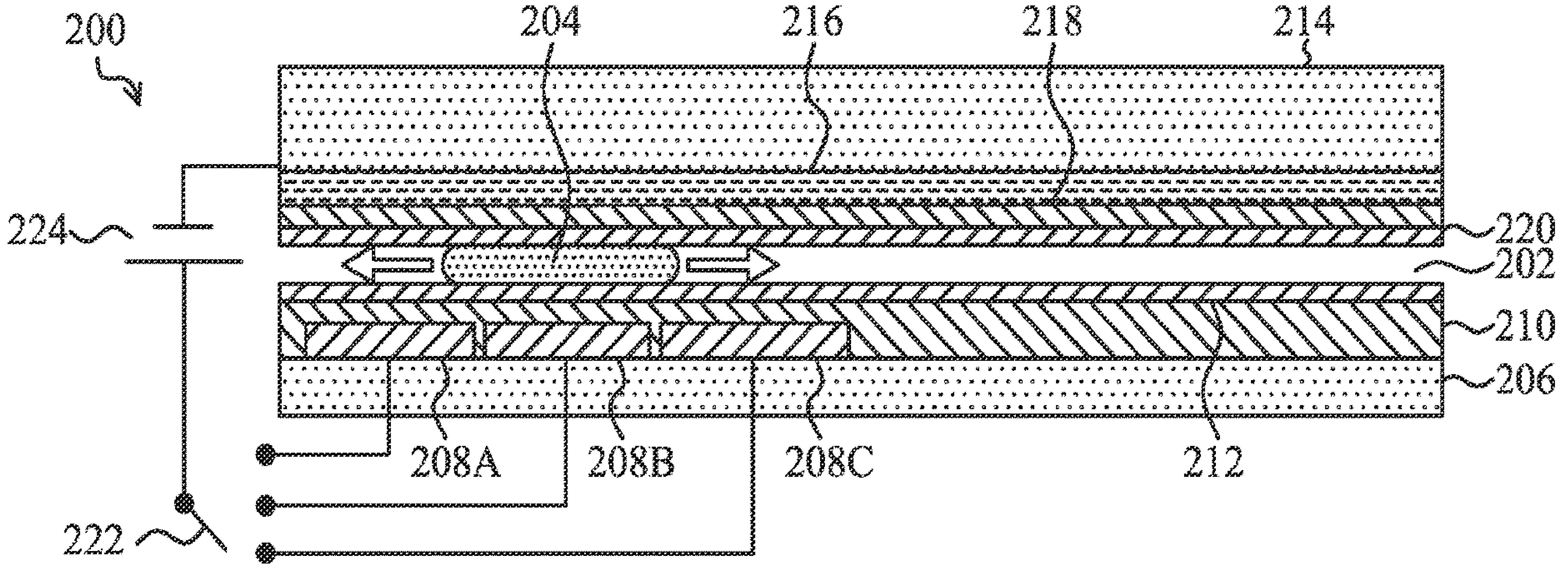
(57) **ABSTRACT**

An integrated semiconductor device for manipulating and processing bio-entity samples and methods are described. The device includes a lower substrate, at least one optical signal conduit disposed on the lower substrate, at least one cap bonding pad disposed on the lower substrate, a cap configured to form a capped area, and disposed on the at least one cap bonding pad, a fluidic channel, wherein a first side of the fluidic channel is formed on the lower substrate and a second side of the fluidic channel is formed on the cap, a photosensor array coupled to sensor control circuitry, and logic circuitry coupled to the fluidic control circuitry, and the sensor control circuitry.

20 Claims, 15 Drawing Sheets



Related U.S. Application Data

continuation of application No. 15/179,637, filed on Jun. 10, 2016, now Pat. No. 10,280,456, which is a continuation of application No. 13/830,234, filed on Mar. 14, 2013, now Pat. No. 9,366,647.

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G01N 21/64	(2006.01)
B01F 33/302	(2022.01)
B01F 33/3031	(2022.01)
G02B 6/122	(2006.01)
G01N 21/03	(2006.01)

(52) **U.S. Cl.**

CPC ... ***B01L 3/502707*** (2013.01); ***B01L 3/502792*** (2013.01); ***G01N 21/05*** (2013.01); ***G01N 21/6428*** (2013.01); ***G01N 27/44721*** (2013.01); ***G01N 27/44791*** (2013.01); *B01L 2300/0654* (2013.01); *B01L 2300/089* (2013.01); *B01L 2300/0819* (2013.01); *B01L 2300/0867* (2013.01); *B01L 2300/165* (2013.01); *B01L 2300/168* (2013.01); *B01L 2400/0427* (2013.01); *G01N 2021/0325* (2013.01); *G01N 2021/058* (2013.01); *G01N 2021/6482* (2013.01); *G01N 2201/08* (2013.01); *G02B 6/122* (2013.01)

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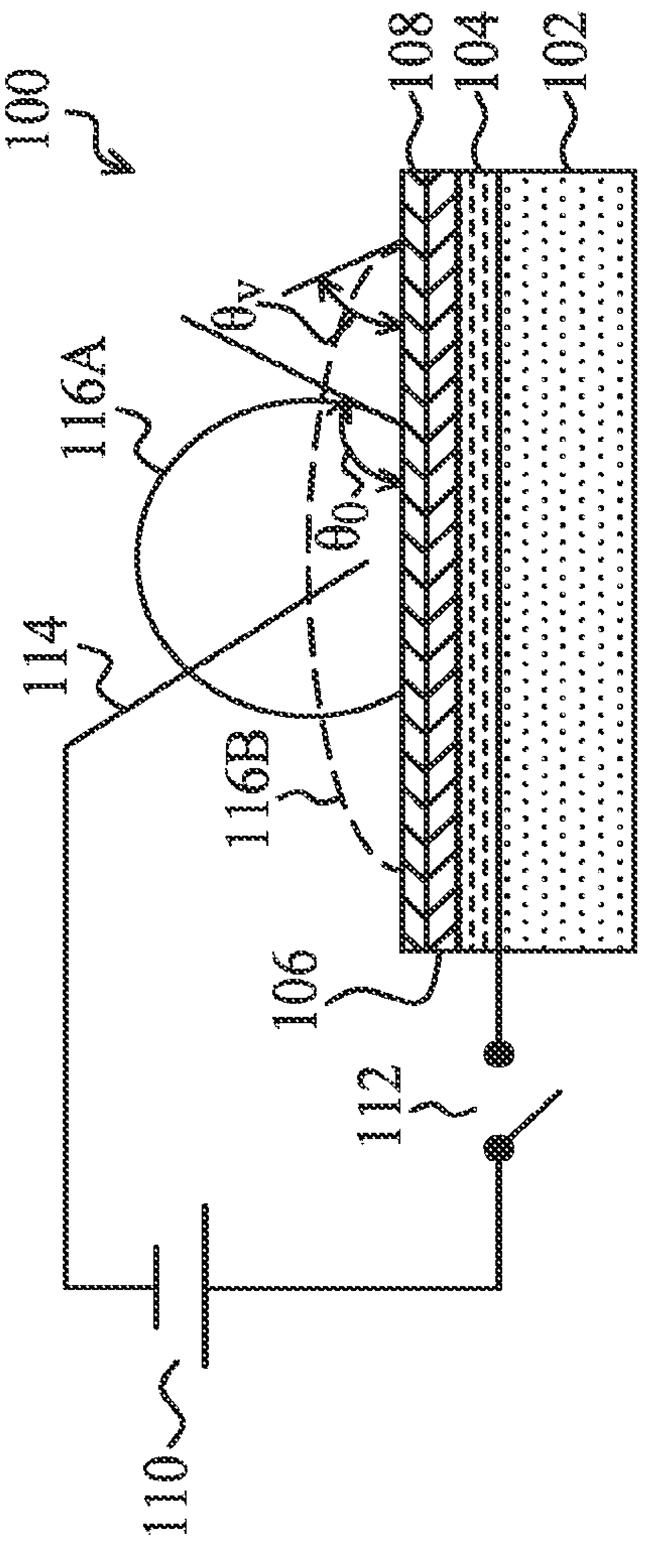
100
108
104
102
116A
θ_V
θ_0
114
116B
106
112
110

FIG. 1

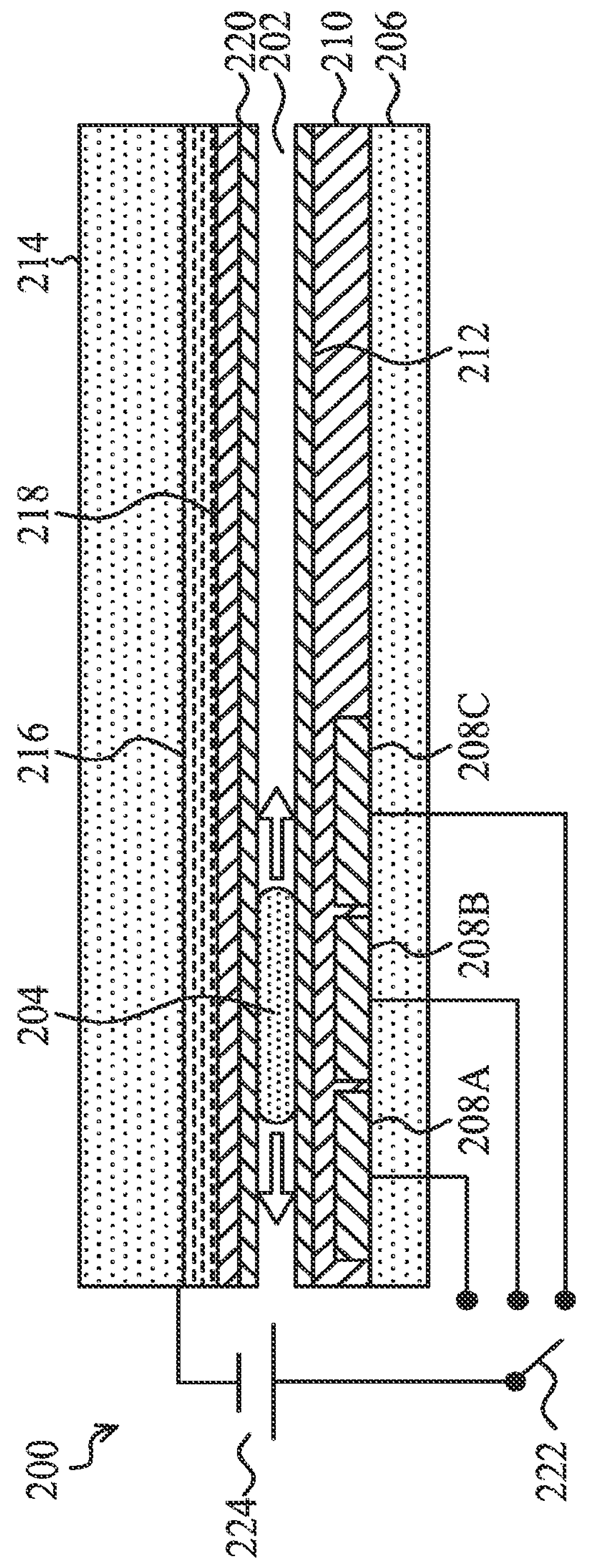
220
202
210
206
214
212
218
216
208C
204
208B
208A
200
224
222

FIG. 2

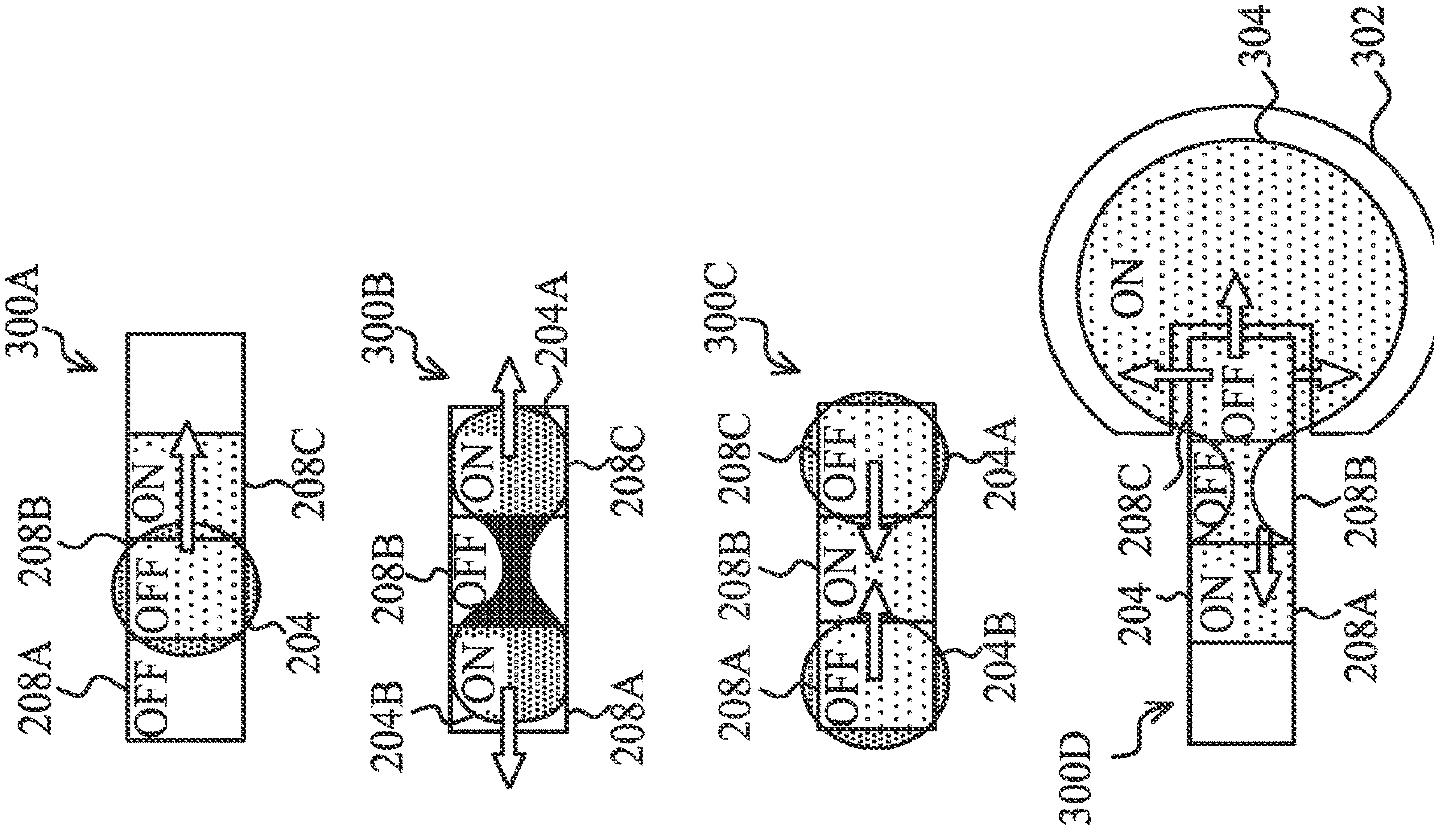
300A
208A
208B
208C
204
OFF
OFF
ON
300B
204B
208B
204A
208C
208A
ON
OFF
ON
300C
208A
208B
208C
204A
204B
OFF
ON
OFF
300D
204
208C
208B
208A
304
302
ON
OFF
OFF
ON

FIG. 3

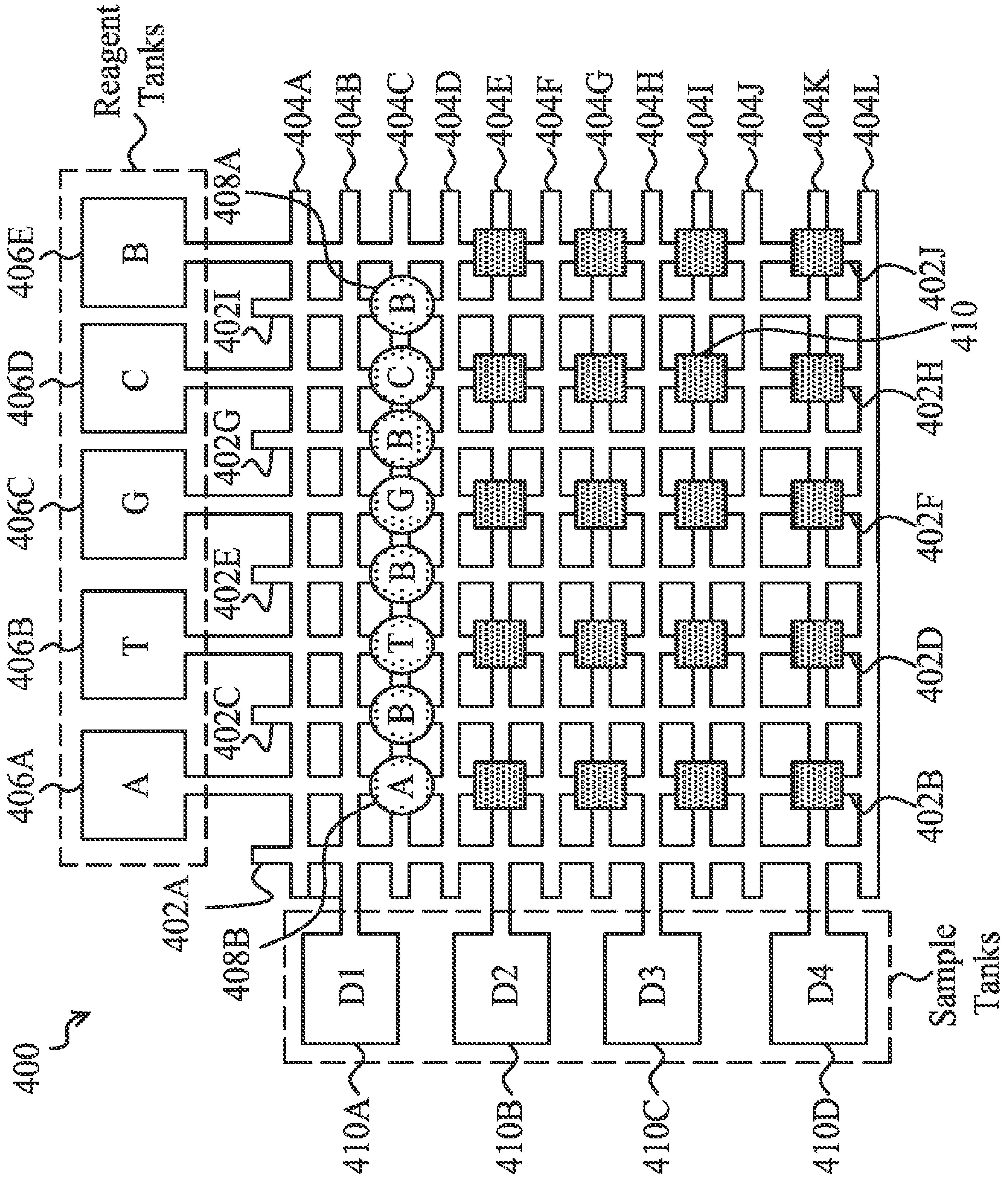
400
Reagent Tanks
406A
406B
406C
406D
406E
A
T
G
C
B
402A
402C
402E
402G
402I
408A
408B
404A
404B
404C
404D
404E
404F
404G
404H
404I
404J
404K
404L
A
B
T
B
G
B
C
B
402B
402D
402F
402H
402J
410
D1
D2
D3
D4
Sample Tanks
410A
410B
410C
410D

FIG. 4

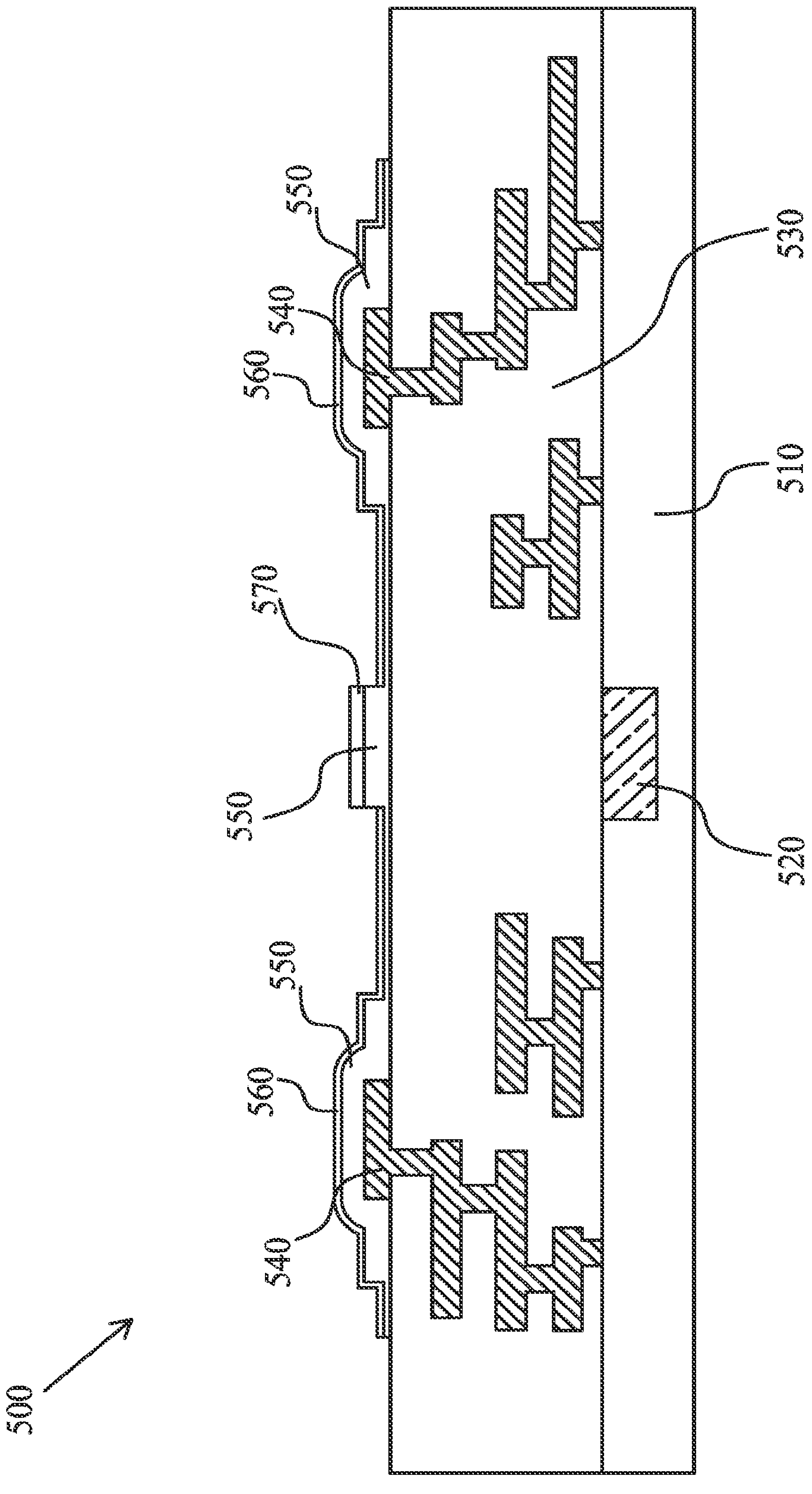

FIG. 5

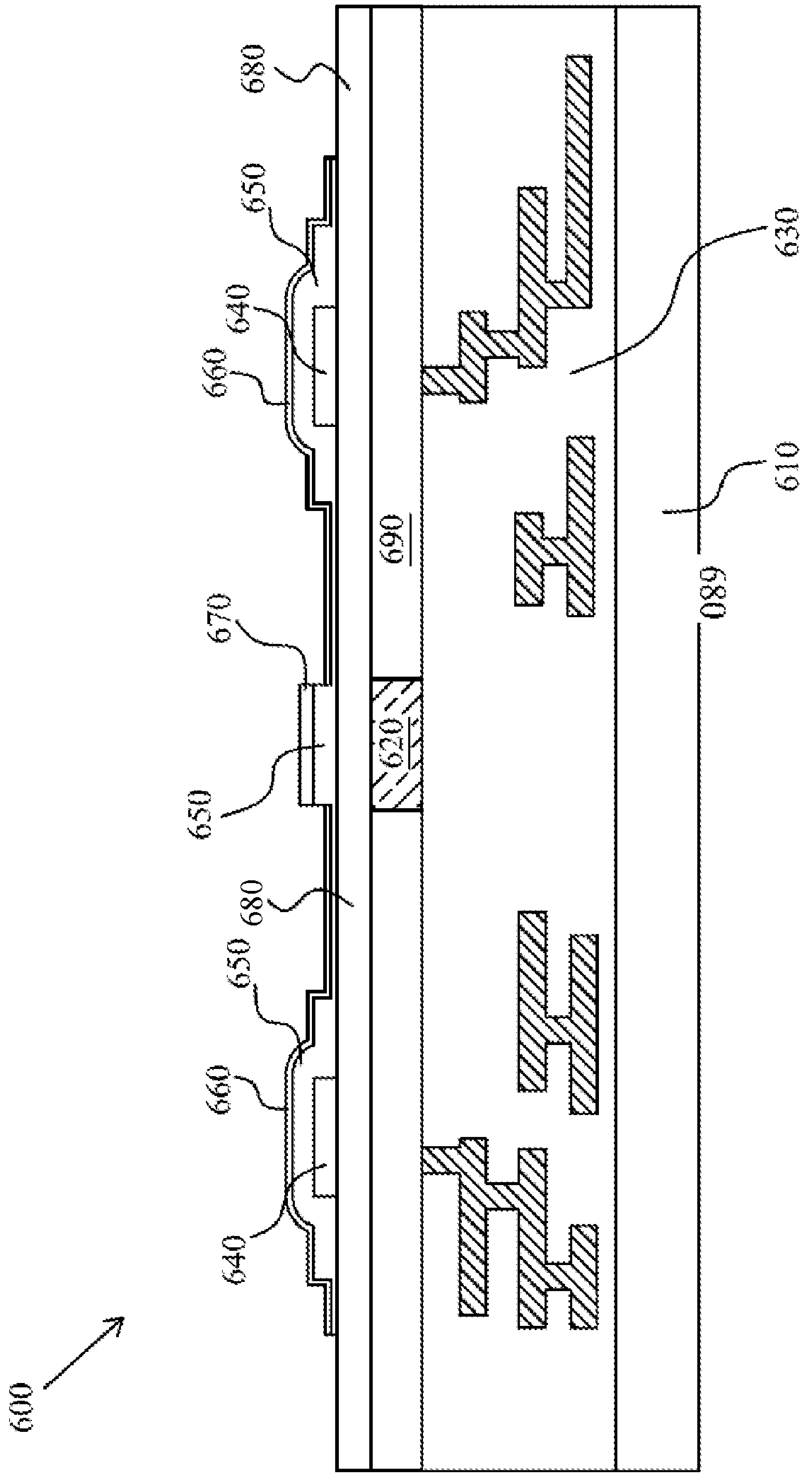

FIG. 6

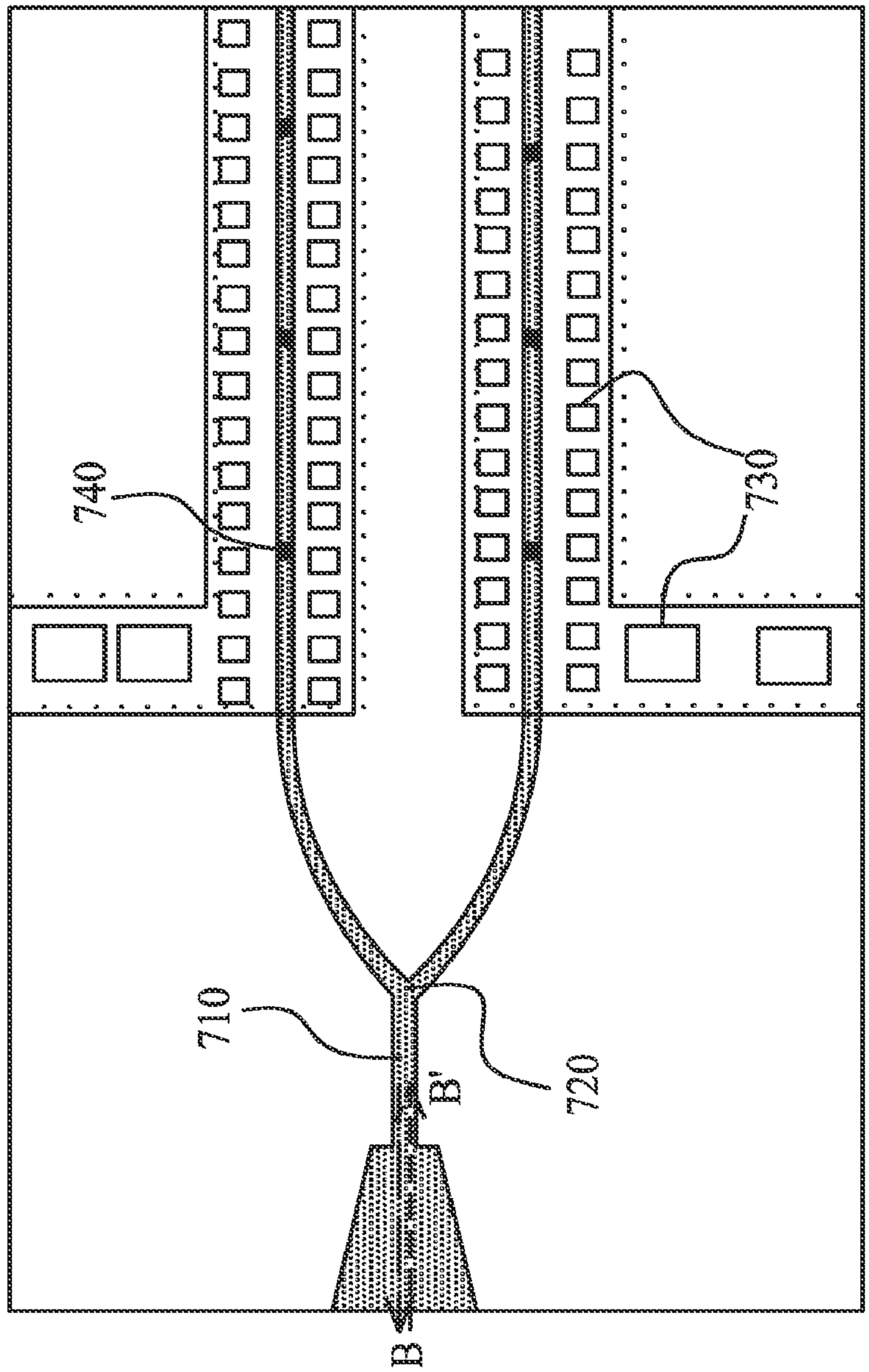

FIG. 7

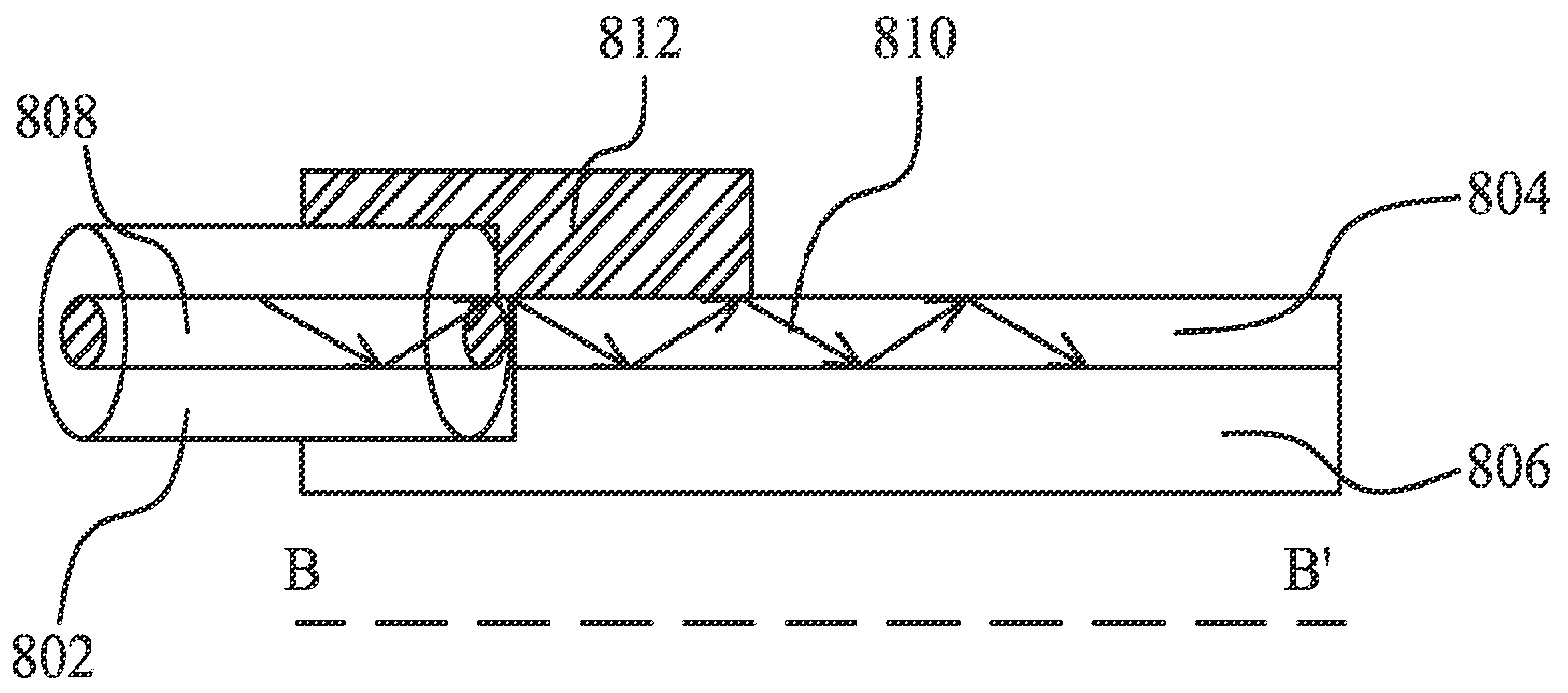

FIG. 8A

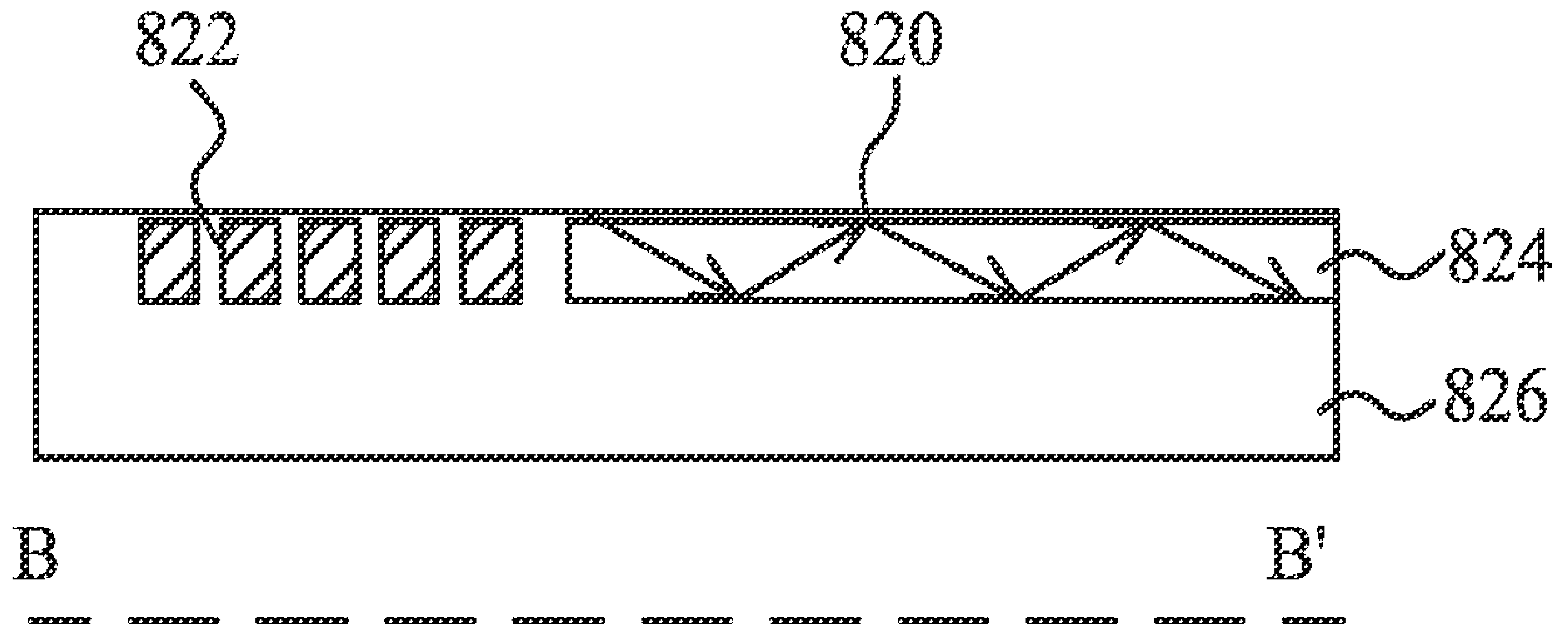

FIG. 8B

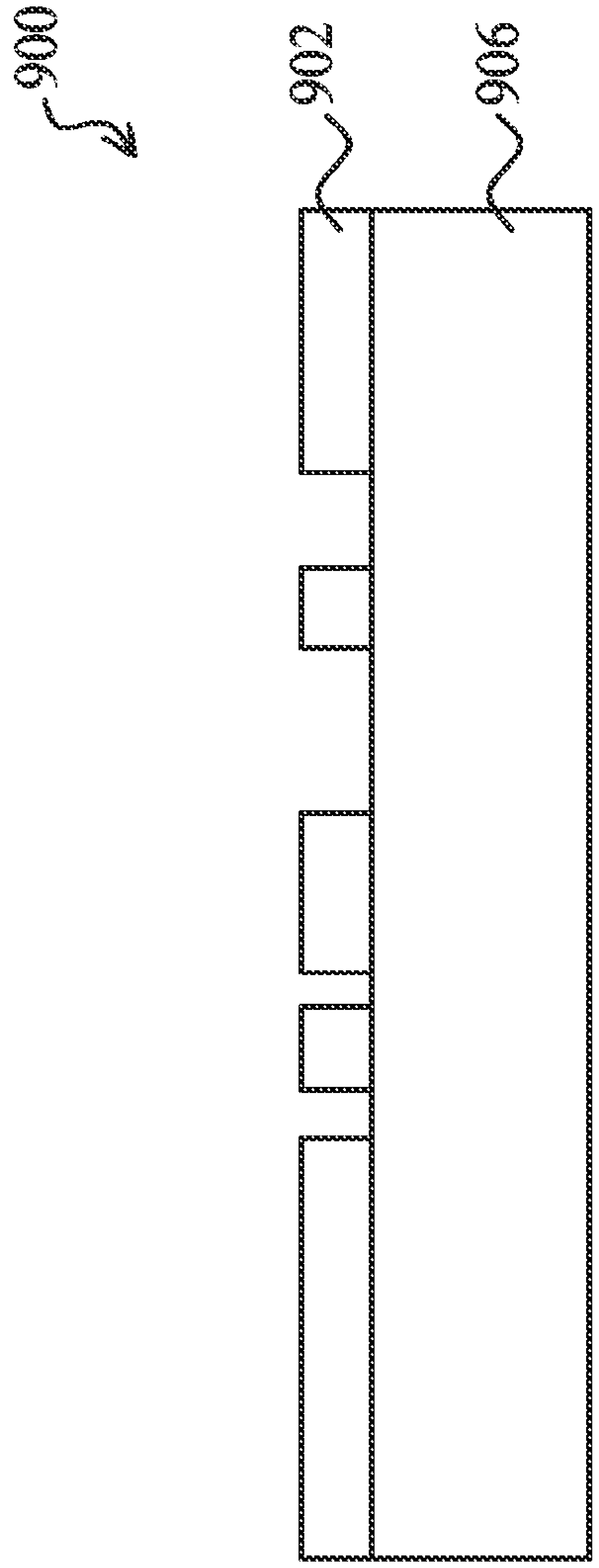

FIG. 9A

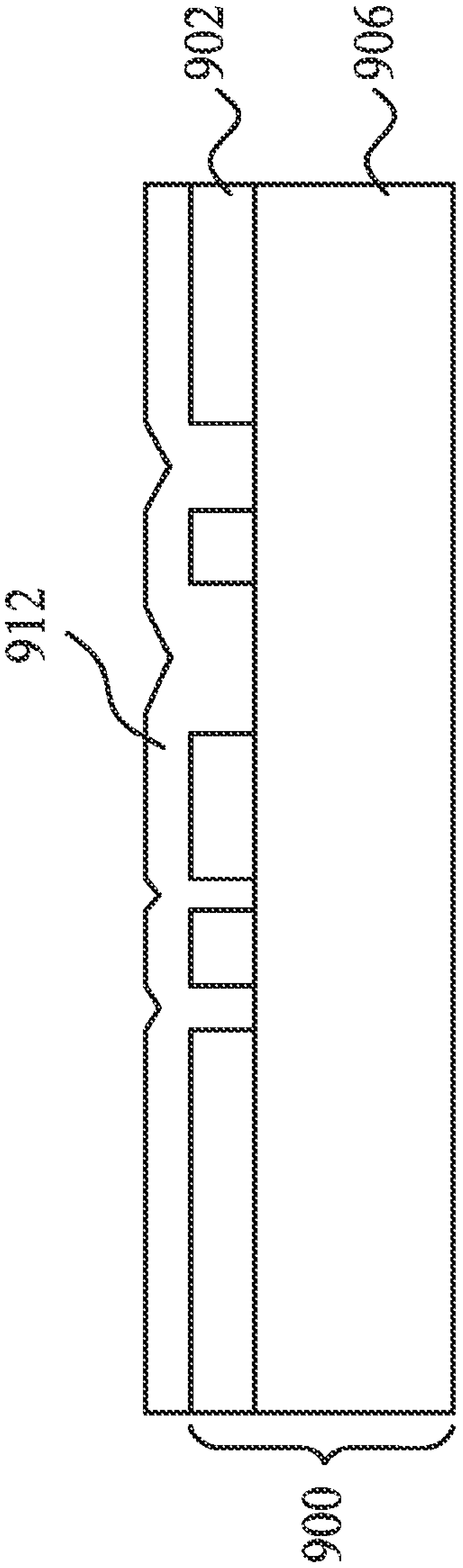

FIG. 9B

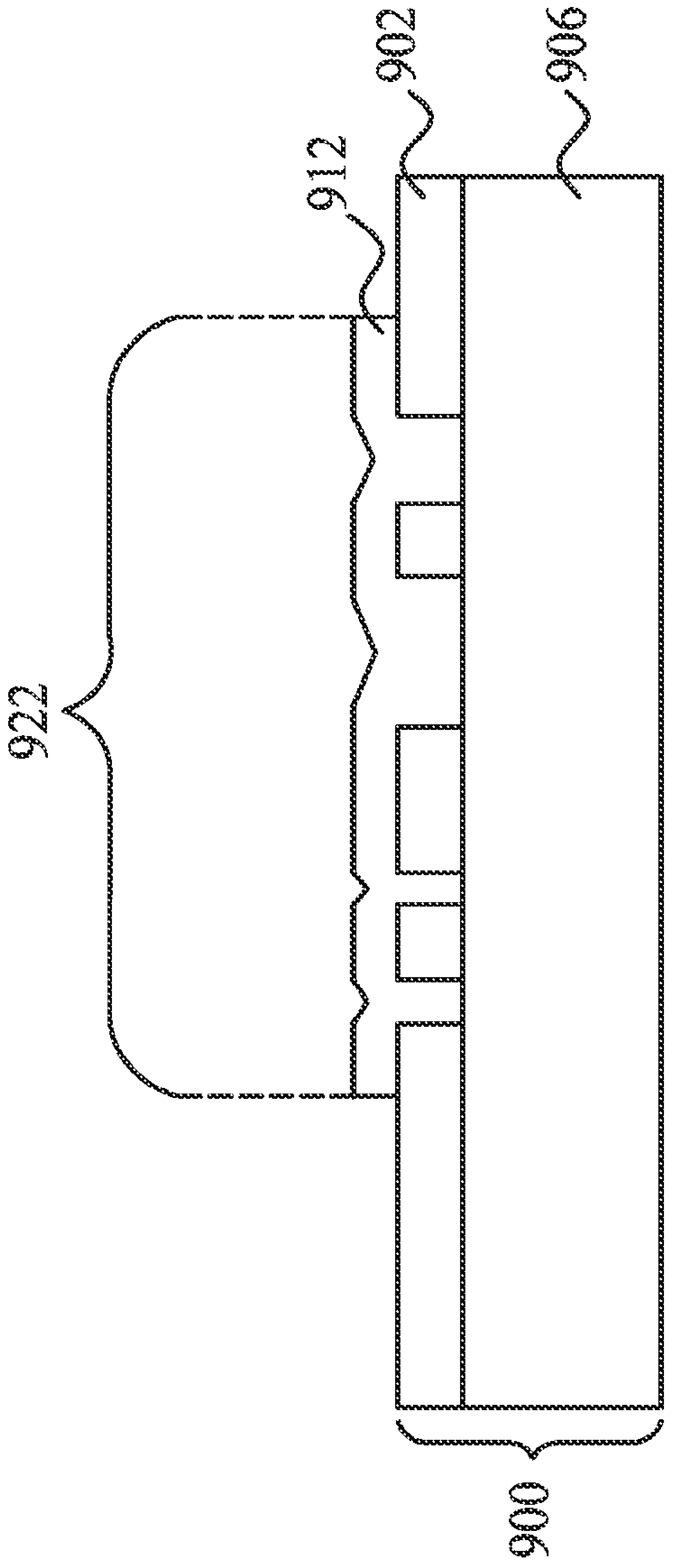

FIG. 9C

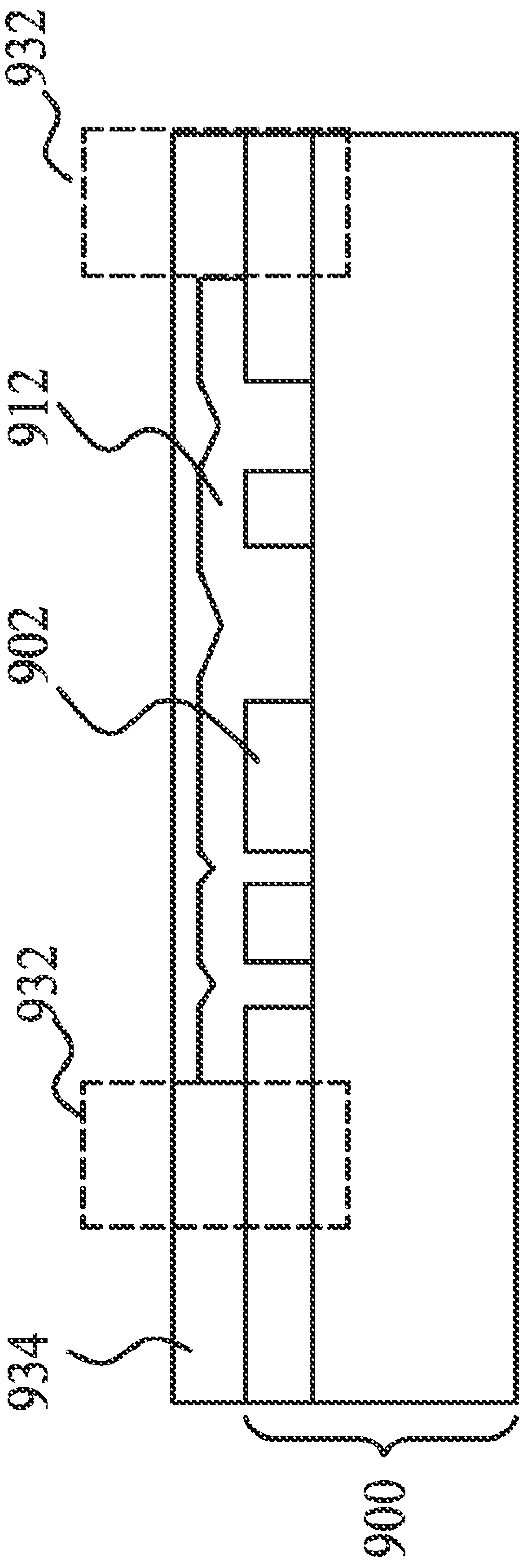

FIG. 9D

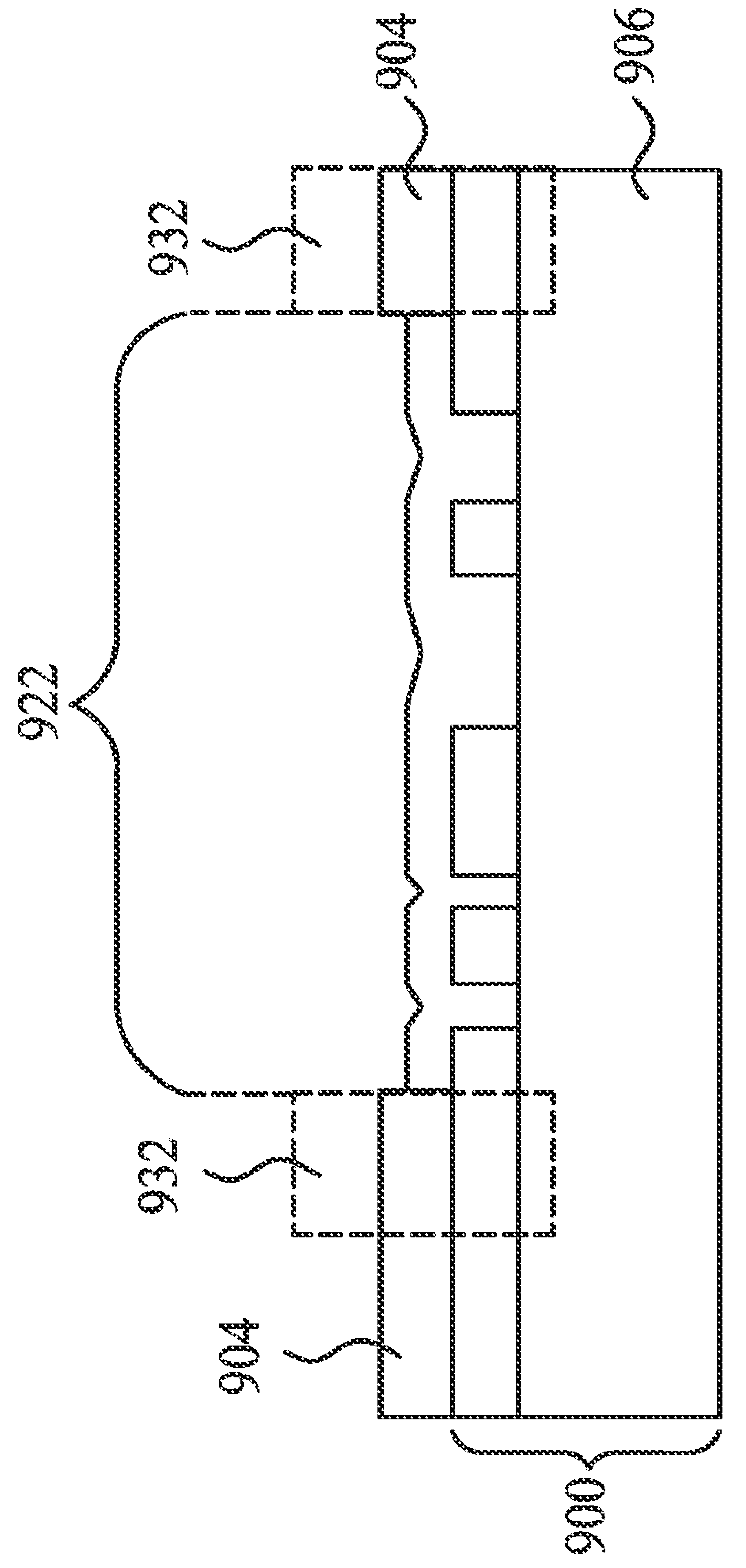

FIG. 9E

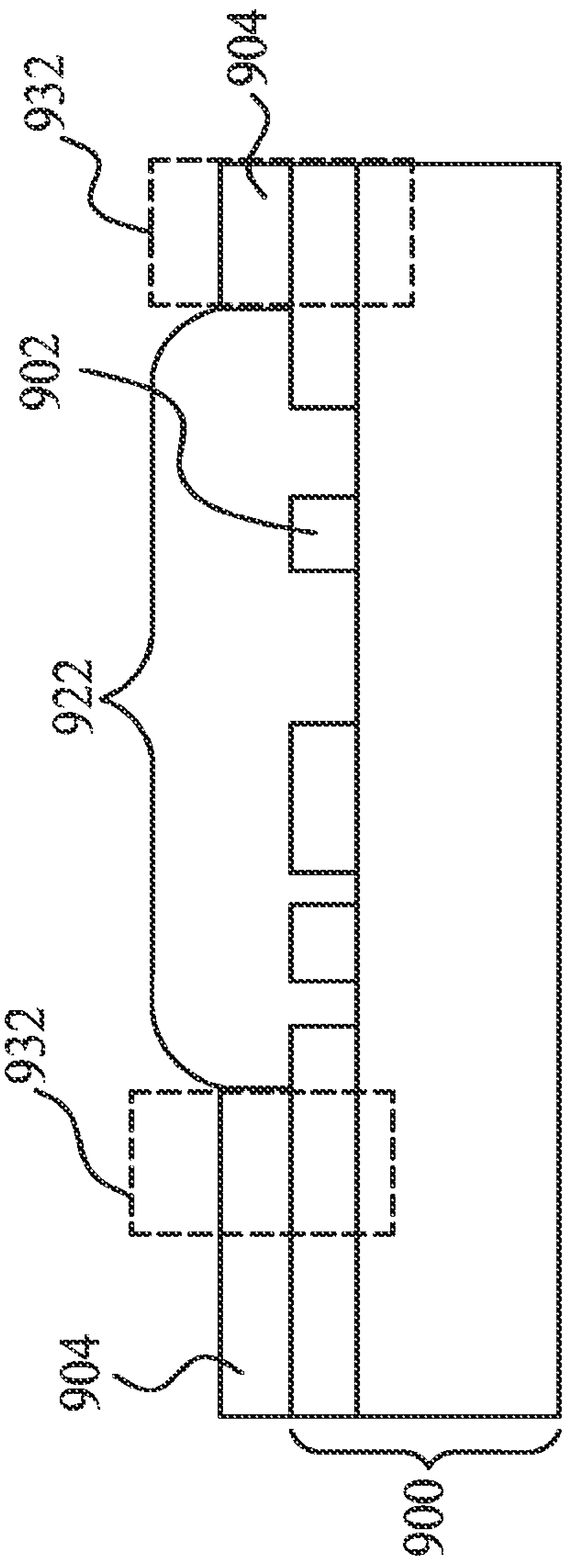

FIG. 9F

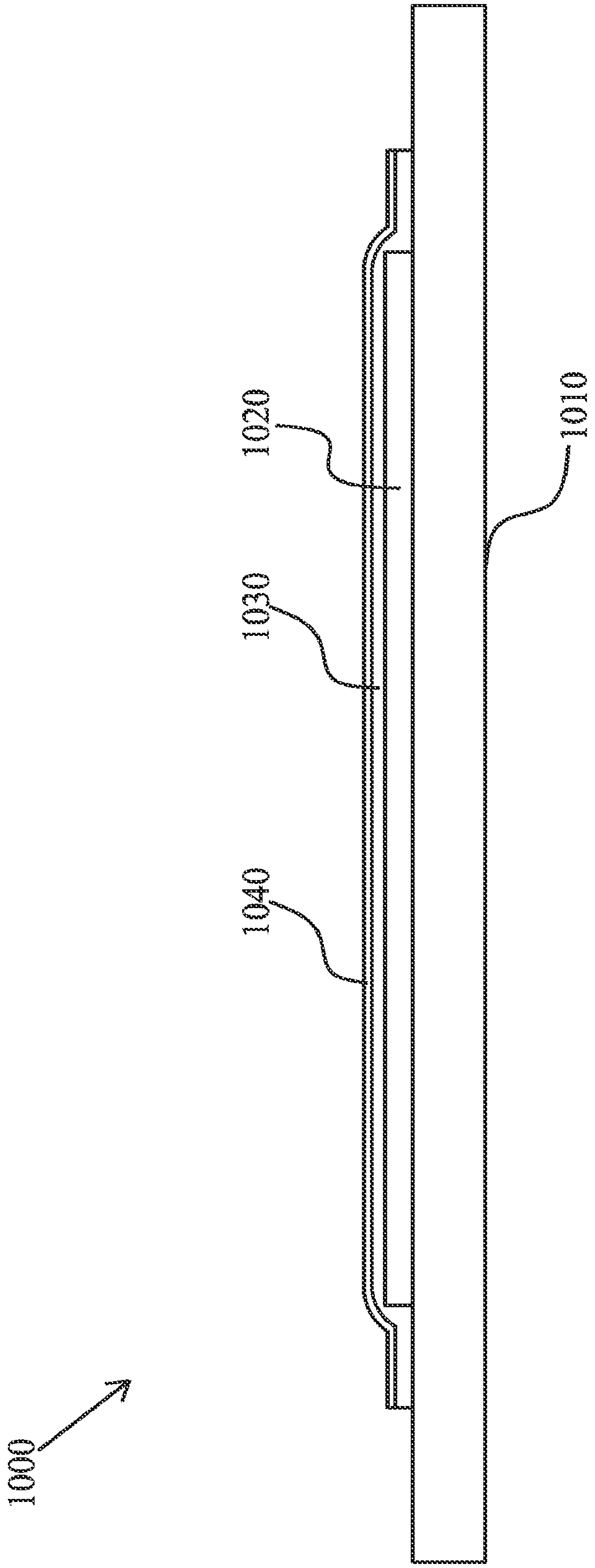

FIG. 10

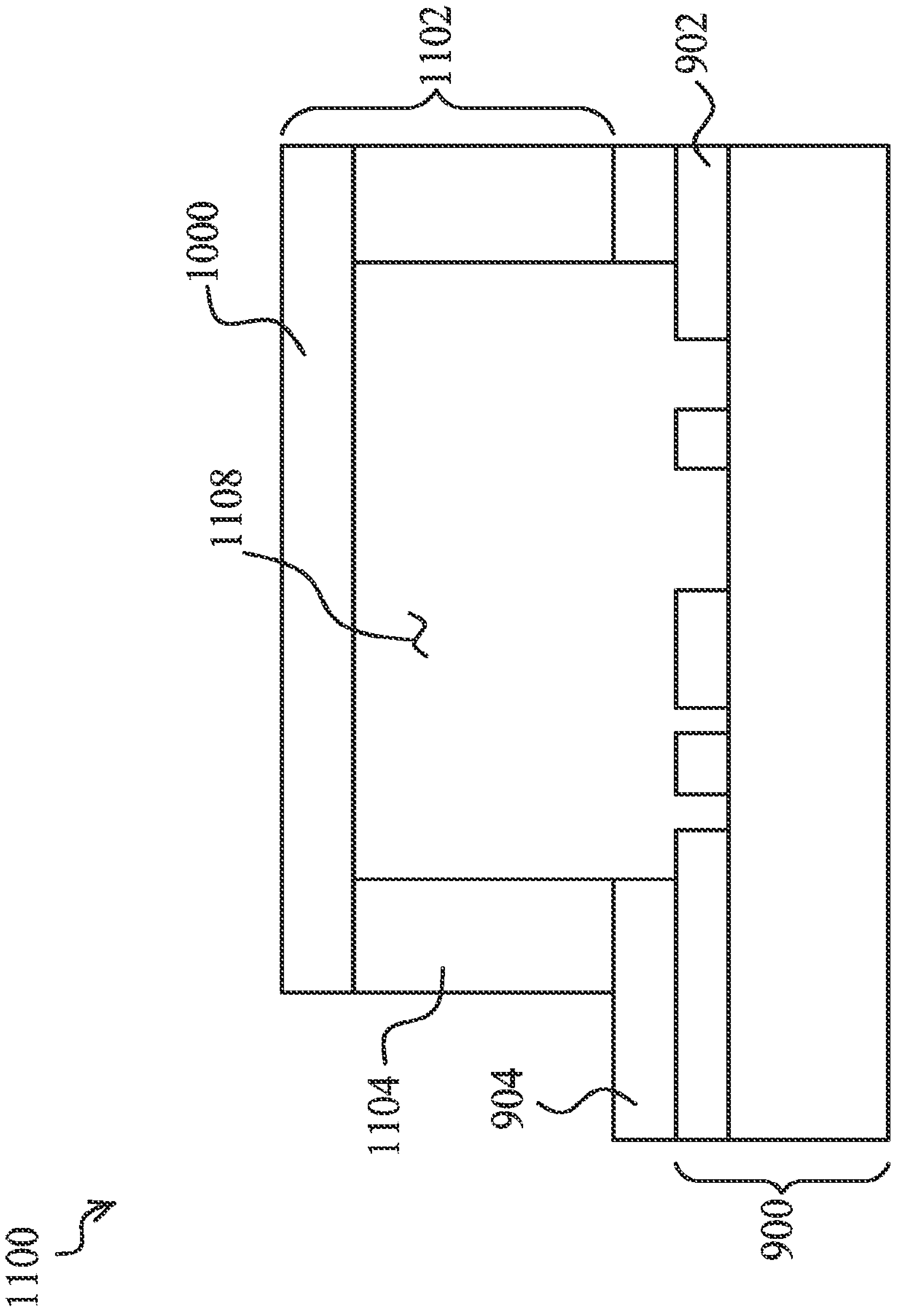

FIG. 11A

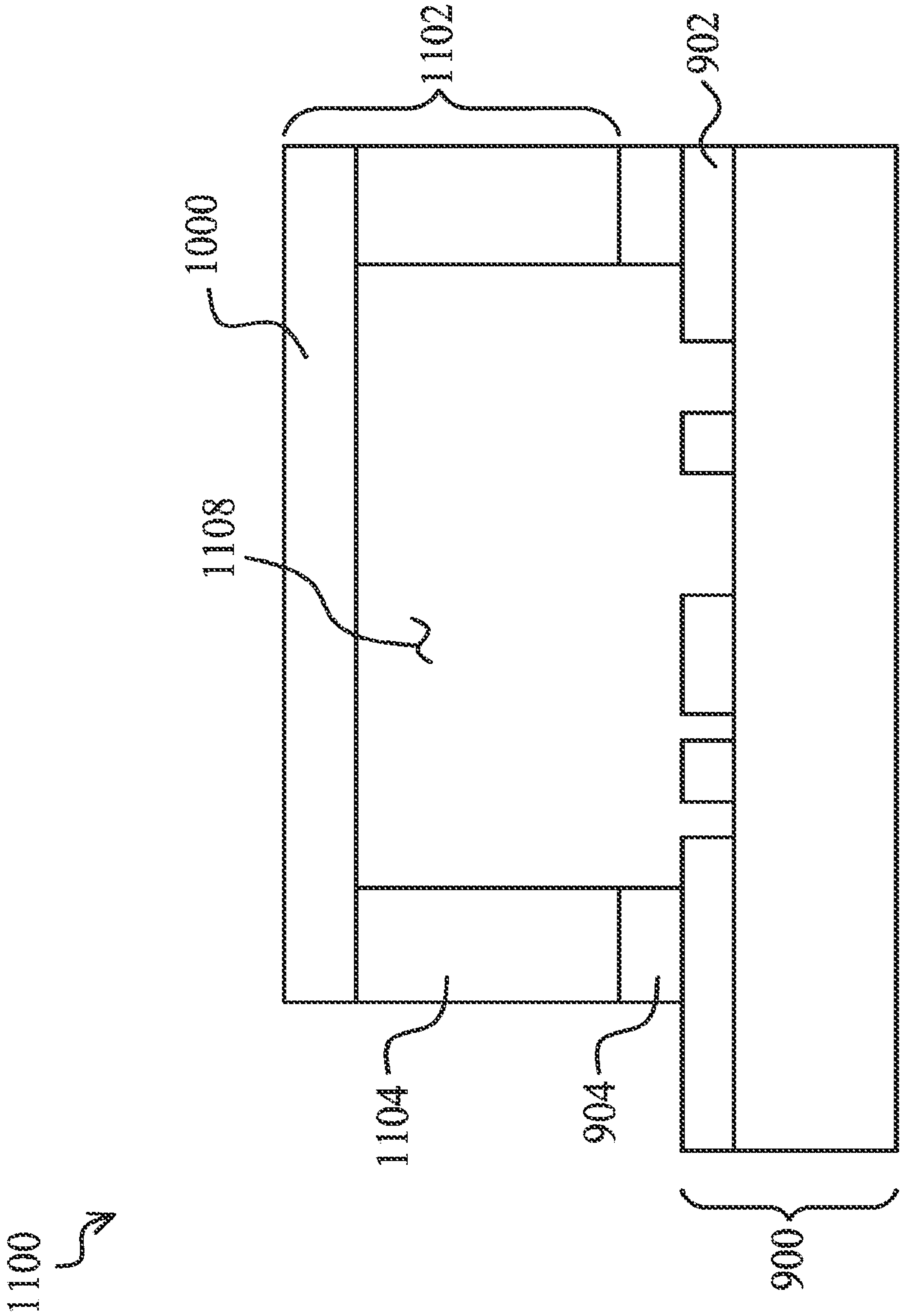

FIG. 11B

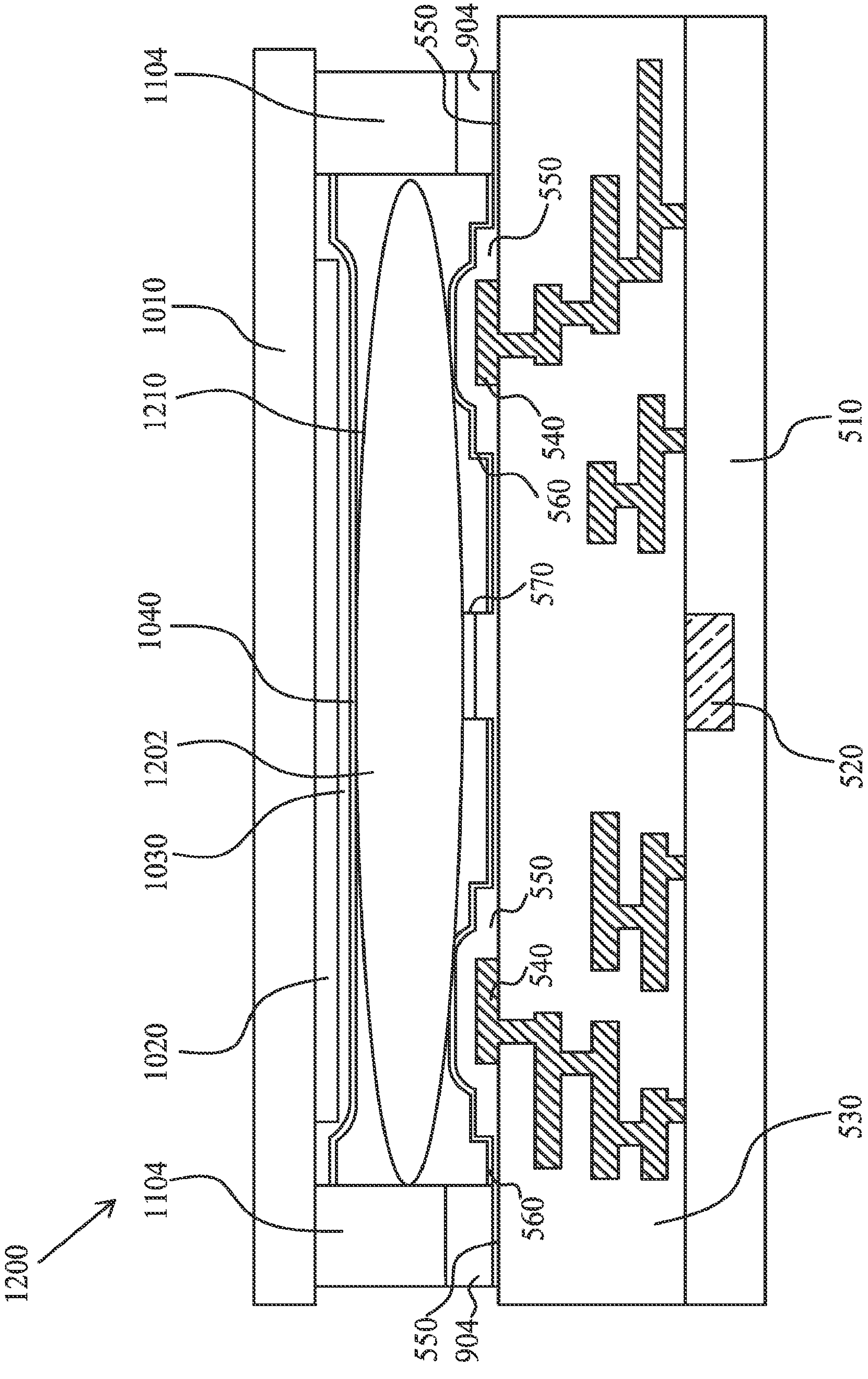
1200
1104
1010
1210
1040
1202
1030
1020
1104
550
904
550
540
560
570
550
540
560
550
904
510
520
530

FIG. 12

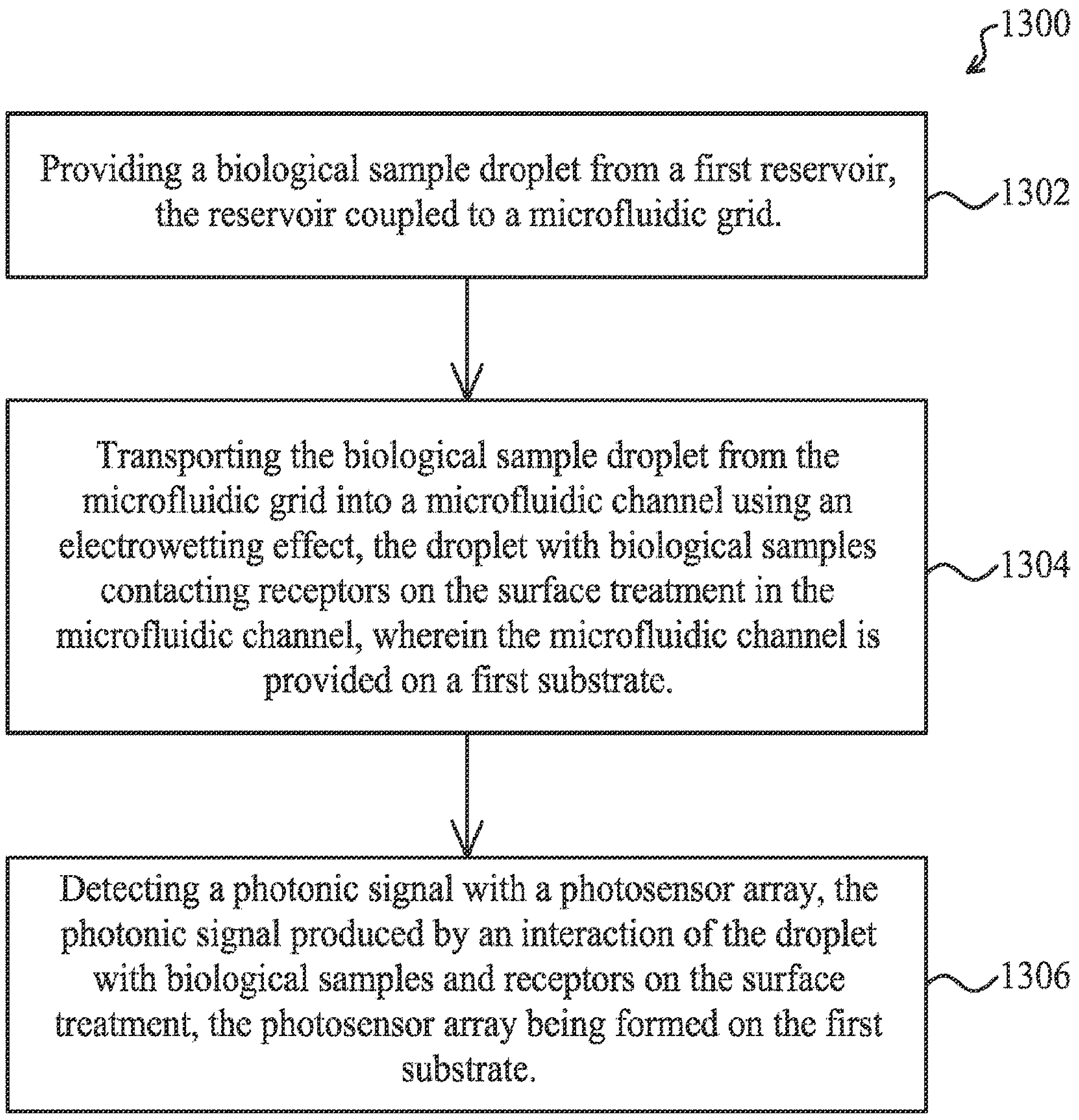
1300
Providing a biological sample droplet from a first reservoir, the reservoir coupled to a microfluidic grid.
1302
Transporting the biological sample droplet from the microfluidic grid into a microfluidic channel using an electrowetting effect, the droplet with biological samples contacting receptors on the surface treatment in the microfluidic channel, wherein the microfluidic channel is provided on a first substrate.
1304
Detecting a photonic signal with a photosensor array, the photonic signal produced by an interaction of the droplet with biological samples and receptors on the surface treatment, the photosensor array being formed on the first substrate.
1306

FIG. 13

OPTICAL DETECTION FOR BIO-ENTITIES

The present application is a continuation of U.S. application Ser. No. 16/403,873, filed on May 6, 2019, which is a continuation of U.S. application Ser. No. 15/179,637, filed Jun. 10, 2016, which is a continuation of U.S. application Ser. No. 13/830,234, filed Mar. 14, 2013, each of which is hereby incorporated by reference in its entirety.

BACKGROUND

Medical technology industries, including device manufactures as well as pharmaceuticals and biologics manufacturers, have experienced significant commercial and technological growth over the past several decades. Since the discovery of DNA, our understanding of its bio-informational role in the development, operation, and interaction of all living beings has significantly increased thanks to the development of DNA sequencing techniques over the years. Through improvement in DNA sequencing detection techniques, scientists and doctors have gained greater insight on diseases as well as more effective treatments for patients based on their genetic dispositions. Thus, the use and role of DNA sequencing results in health care has increased significantly.

DNA sequences are series of the nucleotide bases adenine, guanine, cytosine, and thymine, that dictate the formation of proteins in biological systems. By analyzing a DNA sequence, important information can be gleaned for both diagnostic and therapeutic purposes. Additionally, the identification and quantification of other biological entities (bio-entities), such as proteins, small molecules, and pathogens has pushed forward the potential of medical knowledge to benefit humankind.

Packaged sequencers employing electrowetting-on-dielectric (EWOD) for control use amplification and labeling techniques that allow for optical detection by using fluorescent dyes and external optical systems with analog-to-digital conversion systems to allow for the computer processing required for handling the large amounts of data produced. Many implementations of packaged EWOD sequencers have a glass substrate and a transparent electrode, which can be problematic. For example, light can be transmitted through the glass substrate and into the droplet being analyzed, where sequencing is happening. In such case, transmission may not be efficient because of interference patterns from different transparent index of refractions as well as different thicknesses of transparent material. In addition, the integration of color filters into EWOD sequencers can reduce efficiency of light sent into a sensor array.

Therefore, a need exists for improved bio-entity manipulation devices and processing technologies.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** is a cross-sectional diagram of an EWOD apparatus.

FIG. **2** is a cross-sectional diagram of a fluidic control system that uses electrowetting to transport and manipulate bio-entity sample droplets.

FIG. **3** is a diagram illustrating how certain actions may be achieved using an electrowetting fluidic control system.

FIG. **4** is a diagram of a microfluidic grid for transporting and mixing target bio-entity samples and biological reagents.

FIG. **5** is a cross-sectional diagram of a lower wafer for use in a bio-entity manipulation and processing system according to an embodiment.

FIG. **6** is a cross-sectional diagram of a lower wafer for use in a bio-entity manipulation and processing system according to another embodiment.

FIG. **7** is a top view diagram of a lower wafer for use in a bio-entity manipulation and processing system according to an embodiment.

FIGS. **8**A and **8**B are side view diagrams illustrating optical conduits and optical inputs on a lower wafer for use in a bio-entity manipulation and processing system according to an embodiment.

FIGS. **9**A-**9**F are cross-sectional diagrams illustrating embodiments of a method for forming a lower wafer for use in a bio-entity manipulation and processing system according to an embodiment.

FIG. **10** is a cross-sectional diagram of an upper wafer that may be used in a bio-entity manipulation and processing system according to an embodiment.

FIGS. **11**A and **11**B are side view diagrams illustrating embodiments of bonding a lower wafer and an upper wafer for use in a bio-entity manipulation and processing system according to an embodiment.

FIG. **12** is a cross-sectional diagram of a microfluidic bio-entity manipulation and processing system according to an embodiment.

FIG. **13** is a flowchart of a method for manipulating and processing bio-entity samples with an integrated semiconductor device.

The various features disclosed in the drawings briefly described above will become more apparent to one of skill in the art upon reading the detailed description below.

DETAILED DESCRIPTION

It is to be understood that the following disclosure provides many different embodiments and examples for implementing different features of the invention. Specific examples of components and arrangements are described below to simplify the present disclosure. These are, of course, merely examples and are not intended to be limiting. Moreover, the formation of a first feature over or on a second feature in the description that follows may include embodiments in which the first and second features are formed in direct contact, and may also include embodiments in which additional features may be formed interposing the first and second features, such that the first and second features may not be in direct contact. Various features in the figures may be arbitrarily drawn in different scales for the sake of simplicity and clarity. Where features depicted in the various figures are common between two or more figures, the same identifying numerals have been used for clarity of description. However, this should not be understood as limiting such features.

FIG. **1** is a cross-sectional diagram of an electro-wetting-on-dielectric (EWOD) apparatus **100**. The apparatus **100** includes a substrate **102** with three material layers thereon. These material layers include an electrode layer **104**, a dielectric layer **106**, and a hydrophobic coating **108**. The electrode layer **104** is coupled to a variable voltage source **110** by a switch **112**. Attached to the opposite end of the voltage source **110** is a probe **114**. As depicted in FIG. **1**, the apparatus **100** positions the probe **114** to be inserted into a droplet shown in two different states. Droplet **116**A depicts the droplet in a state when no voltage is being applied by probe **114**. Because of the hydrophobic coating **108**, droplet

116A has a contact angle θ_0 as shown. By applying a voltage from the voltage source **110** through the probe **114**, the contact angle can be decreased and the contact area increased. Thus, droplet **116**B is the droplet when a voltage is applied. The contact angle is then decreased to θ_v, bringing the mass of the droplet **116**B closer to the underlying electrode layer **104**. The change in the contact angle caused by the applied voltage is related to the applied voltage according to equation (1) below.

$$\cos\theta_V - \cos\theta_0 = \frac{\varepsilon\varepsilon_o}{2\gamma_{LG}t}V^2 \tag{1}$$

In equation (1), V is the applied electrical potential or voltage, θ_v is the contact angle under applied voltage V, and θ_0 is the contact angle without applied voltage V. Other variables include: E, the dielectric constant of the dielectric layer **106**; ε_0, the vacuum permittivity; γ_{LG}, the surface tension; and t, the thickness of dielectric layer **106**. This manipulation of the apparent hydrophobicity of the droplet in apparatus **100** may be referred to as electrowetting-on-dielectric (EWOD). Thus, by using EWOD, the physical configuration of a droplet on a hydrophobic surface can be altered and controlled as seen in FIG. **1**.

FIG. **2** is a cross-sectional diagram of a fluidic control system **200** that allows for transporting and manipulating bio-entity sample droplets using EWOD principles. The fluidic control system **200** operates around a microfluidic channel **202** to control a droplet **204** within the channel. Droplet **204** is a bio-entity sample droplet. A "bio-entity" or "biological entity" as used herein may refer to DNA, RNA, a protein, a small molecule, a virus or other pathogen, or any such thing that may be sequenced, identified, or quantified. Such activities may take place in a medical or industrial context. Throughout the disclosure, the example of DNA sequencing is presented; however, the embodiments are not limited to this example.

As seen in FIG. **2**, the bottom portion of the microfluidic channel **202** is provided by a lower substrate **206** with several layers thereon. These layers include three electrodes **208**A, **208**B, and **208**C, which are surrounded by a first dielectric layer **210**. Above the dielectric layer **210** is a first hydrophobic coating **212** that provides the lower surface of the microfluidic channel **202**.

The top surface of the microfluidic channel **202** is provided by another hydrophobic coating, which is formed over a upper substrate **214**. This upper substrate **214** is a substrate upon which several material layers are deposited. These layers include a top electrode layer **216**, a second dielectric layer **218**, and a second hydrophobic coating **220**, which forms the top surface of the microfluidic channel **202**. The upper substrate **214** is inverted and brought close to the surface of the first hydrophobic coating **212**. Thus, the droplet **204** is physically bounded by the first hydrophobic coating **212** on the bottom and the second hydrophobic coating **220** on the top.

The bottom electrodes **208**A, **208**B, and **208**C are coupled to a switch **222** capable of selecting any combination of these three electrodes. The switch **222**, in turn is connected to a voltage source **224**, the opposite side of which is connected to the top electrode layer **216**. By selectively applying a voltage to various combinations of electrodes **208**A, **208**B, and **208**C, the electric field in which the droplet **204** is located can be altered. In the depicted embodiment a DC potential is applied, but in other embodiments, an AC potential may be used instead. By controlling the electric fields between the bottom electrodes **208**A, **208**B, and **208**C and the top electrode **216**, the droplet **204** itself can be manipulated and transported in various ways. This can be better understood by reference to FIG. **3**.

FIG. **3** is a diagram illustrating how certain actions may be achieved using an EWOD fluidic control system. Four exemplary actions are depicted: a lateral movement **300**A, a droplet split **300**B, a droplet merger **300**C, and a droplet formation **300**D. These examples depict actions performed in the fluidic control system **200** as seen from above, looking down onto the droplet **204** through substrate **214**.

As depicted in the lateral movement **300**A, the droplet **204** is situated above the electrode **208**B. When switch **222** is asserted so that bottom electrode **208**A is disconnected from the voltage source **224** (OFF), bottom electrode **208**B is OFF, and bottom electrode **208**C is connected to the voltage source **224** (ON), the droplet moves in the direction of electrode **208**C until it is located over electrode **208**C.

As depicted in the droplet split **300**B, droplet **204** begins situated above bottom electrode **208**B. When switch **222** is asserted so that the bottom electrode **208**B is OFF and both bottom electrodes **208**A and **208**C are ON, the portion of the droplet **204** that is closest to bottom electrode **208**A will move to the left and the portion of the droplet **204** that is closest to bottom electrode **208**C will move to the right, causing the droplet **204** to be split into a droplet **204**A situated over the bottom electrode **208**C and a droplet **204**B situated over the bottom electrode **208**A.

As depicted in the droplet merger **300**C, the droplet **204**A begins situated above **208**C and the droplet **204**B begins situated over **208**A. When the switch **222** is asserted so that bottom electrodes **208**A and **208**C are OFF and the bottom electrode **208**B is ON, the droplets **204**A and **204**B both move toward the bottom electrode **208**B. The droplets **204**A and **204**B will merge over the bottom electrode **208**B to form a single droplet.

A droplet formation **300**D is also depicted in FIG. **3**. Droplet formation **300**D depicts the formation of a bio-entity sample droplet from a larger bio-entity sample drop. The performance of droplet formation **300**D uses the three bottom electrodes **208**A, **208**B, and **208**C, as discussed, and further includes a larger electrode **302**. The larger electrode **302** may allow for the placement of a larger volume of liquid in a drop **304**. In order to form a droplet **204**, all four electrodes (**302**, **208**A, **208**B, and **208**C) are turned ON to pull the drop **304** out along the path indicated by the square bottom electrodes, then bottom electrodes **208**B and **208**C are turned OFF. The liquid over bottom electrodes **208**B and **208**C is pulled away by the ON state of the other electrodes, and pushed away by the hydrophobicity of the bottom electrodes **208**B and **208**C in their OFF state. The portion of drop **304** above **208**A remains to form droplet **204**.

These examples assume that any other adjacent electrodes are OFF. The lateral movement **300**A, the droplet split **300**B, the droplet merger **300**C, and the droplet formation **300**D actions may be used to manipulate and transport droplets as they move through the microfluidic channel **202** of FIG. **2**, and also through a microfluidic grid.

FIG. **4** is a diagram of a microfluidic grid **400** for transporting and mixing target bio-entities or molecules. For example microfluidic grid **400** may be used for transporting and mixing target DNA samples and biological reagents. The microfluidic grid includes a plurality of horizontal and vertical paths lined by electrodes like the electrodes **208**A, **208**B, and **208**C of FIG. **2**. Actions like those described in connection with FIG. **3** may be used to move, split, merge, and form droplets in the microfluidic grid **400**.

The plurality of vertical paths is labeled as vertical paths **402**A-J, while the plurality of horizontal paths is labeled as horizontal paths **404**A-L. Each of vertical paths **402**A-J and each of horizontal paths **404**A-L may be formed from a plurality of linearly arranged electrodes. The spaces in between the vertical paths **402**A-J and the horizontal paths **404**A-L may be empty space as the hydrophobic coatings **212** and **220** may effectively bar a droplet from "jumping" from one hydrophilic path to another with electrodes in an ON state. In some embodiments, material barriers exist in the spaces between the paths.

The microfluidic grid **400** also includes a plurality of tanks from which droplets are introduced into the plurality of paths. Arranged along the top are a number of reagent tanks **406**A-E. In the depicted embodiment of microfluidic grid **400**, these reagent tanks include an adenine reagent tank **406**A, a thymine reagent tank **406**B, a guanine reagent tank **406**C, a cytosine reagent tank **406**D, and a buffer tank **406**E. Other embodiments of microfluidic grid **400** may include other biological reagents. Droplets may be dispensed into the microfluidic grid **400** through vertical paths **402**B, **402**D, **402**F, **402**H, and **402**J, and by selectively asserting the electrodes that make up the horizontal and vertical paths, these droplets may be positioned any where in the microfluidic grid **400** and divided and mixed, or merged, with other droplets. A number of reagent droplets, including exemplary buffer droplet **408**A and exemplary adenine reagent droplet **408**B, are depicted along horizontal path **404**C.

Depicted on the left-hand side of microfluidic grid **400** is a number of bio-entity sample tanks **410**A-D. In the depicted embodiment, used for DNA sequences, each bio-entity sample tank contains a different target DNA fragment, labeled as D1 in target DNA fragment tank **410**A, D2 in target DNA fragment tank **410**B, D3 in target DNA fragment tank **410**C, and D4 in target DNA fragment tank **410**D. In embodiments used for DNA sequencing these tanks hold fragments of a DNA sample to be sequenced. In embodiments used for diagnosis, other types of bio-entity samples, such as antibodies, may be present in the sample tanks.

Sequencing the entire genome of a person or pathogen in a single sequence would require a prohibitively long amount of time. By fragmenting a DNA sample into many samples, each sample may be processed simultaneously in order to decrease the total time required to obtain the entire sequence. The fragments should be labeled beforehand so that the individual parallel sequencing can be recombined. Each square in FIG. **4** is a target DNA fragment, such as exemplary target DNA fragment **410**, that can be manipulated as described above in connection with FIG. **3**, including being mixed with a reagent droplet for tagging. The area underneath the microfluidic grid **400** includes a light sensor array, which may be used to take light-based measurements in order to sequence the target DNA fragment samples. This may be better understood with reference to FIG. **5**.

FIG. **5** is a cross-sectional diagram of a lower wafer **500** having a lower substrate **510** for use in a microfluidic bio-entity manipulation and processing system. The lower substrate **510** includes a fluidic control circuitry area, a solid-state based photosensor area, a logic circuitry area, and a microfluidic channel area. The circuitry and photosensor areas are formed on or in the lower substrate **510**. As depicted, lower substrate **510** is a silicon substrate. However, in other embodiments, lower substrate **510** may be a substrate formed from another suitable elementary semiconductor, such as diamond or germanium; a suitable compound semiconductor, such as silicon carbide, indium arsenide, or indium phosphide; or a suitable alloy semiconductor, such as silicon germanium carbide, gallium arsenic phosphide, or gallium indium phosphide.

The fluidic control circuitry area includes fluidic control circuitry, which includes a plurality of metallization layers connected with associated transistors and other circuit components. The sensor area includes a photosensor array **520** and photosensor control circuitry. In the depicted embodiment, the photosensor array **520** is an array of transistor-based photosensors and is a CMOS image sensor array. However, in other embodiments the photosensor array **520** may include photodiodes, active pixel sensors, phototransistors, photoresistors, charged coupled devices, or the like. The photosensor array **520** is controlled by the photosensor control circuitry, which also includes a plurality of transistors and other circuit components. Finally, in the logic circuitry area, there is a significant amount of logic circuitry, including transistors and other circuit components. The logic circuitry allows for input to and output from the lower substrate **510**. Further logic circuitry is coupled to both the photosensor control circuitry and the fluidic control circuitry, to provide both with signal processing for optimal operation, such as analog-to-digital and digital-to-analog conversion. Fluidic control circuitry, photosensor control circuitry, and logic circuitry are embedded in an inter-level dielectric layer (ILD) **530**.

On top of the ILD **530**, is a plurality of bottom electrodes, much like the bottom electrodes of FIG. **2**. In FIG. **5**, two bottom electrodes **540** are depicted. Many more electrodes may be present in practice, but the two depicted are adequate for clear discussion of lower substrate **510**. In the depicted embodiment, bottom electrodes **540** are made from an aluminum-copper alloy. However, in other embodiments different materials may be used that are also suitable for electrodes. Bottom electrodes **540** are solid rectangles as viewed from above. The bottom electrodes **540** are in communication with the fluidic control circuitry, and thus all may be in an ON or OFF state as described in connection with FIG. **3**.

On top of and surrounding the sides of bottom electrodes **540** is a dielectric layer **550**. In the depicted embodiment, dielectric layer **550** is a high-k dielectric layer formed by an atomic layer deposition (ALD) process, or a chemical vapor deposition (CVD) process, then followed by an annealing process. Over the dielectric layer **550** is a hydrophobic coating **560**. In the depicted embodiment, hydrophobic coating **560** is made from polytetrafluoroethylene (PTFE), while in other embodiments it is a self-assembled monolayer.

A portion of the dielectric layer **550** has been treated with a surface treatment to create a surface treated area **570**. In the depicted embodiment, the surface treated area **570** may contain receptors to promote DNA sequencing, while in other embodiments, a surface treatment with antibody binding receptors may be applied. The surface treated area **570** allows identifiable reactions to take place that give of light when a droplet containing components that react with the particular receptors are brought into contact with the surface treated area **570**. For example, a molecular tag may be added onto base pairs that combine with the target DNA fragment, releasing the tag upon combination, with the release of the tag emitting a light signal.

FIG. **6** illustrates another embodiment of a lower wafer **600**, that allows the photosensor array **620** to be closer to the surface treated area **670**. In between photosensor array **620** and the surface treated area **670** is an oxide or anti-reflecting coating (ARC) layer **680**. The photosensor array **620** is on another substrate **690**, which may be silicon. Like the lower wafer **500**, the lower wafer **600** also includes ILD **630**, bottom electrodes **640**, dielectric layer **650**, and hydrophobic coating **660**.

FIG. **7** illustrates a top view of the upper wafer **500** or **600**. The dielectric layer **550** and **650** is formed on the lower substrate **510** and **610** and functions as an optical signal conduit or waveguide **710** with input structures configured to couple an input source to the optical signal conduit **710**. Attached to the optical signal conduit **710** is a waveguide splitter **720** for splitting the optical signal conduit **710** into different pathways. Although the waveguide splitter **720** is shown splitting the optical signal conduit **710** into two pathways, it should be understood that more than two pathways may be formed by the waveguide splitter **720**. Also shown are electrodes **730** covered in the dielectric layer **550** or **660** and hydrophobic coating **560** and **660**, and surface treated area **740**. Many other suitable electrode configurations may be used besides the one shown.

FIGS. **8**A and **8**B show the optical signal conduit along the line B-B' in FIG. **7**. FIG. **8**A illustrates an optical cable **802** input. The optical signal conduit **804** is formed on the substrate **806**. The optical cable **802** may be attached to the substrate **806** so that an optical core **808** of the optical cable **802** provides an optical path for incoming light **810** to the optical signal conduit **804**. The optical cable **802** may be attached and held in place by an adhesive **812** such as polydimethylsiloxane (PDMS), by an adhesive fastening system, or by any other suitable attachment system

FIG. **8**B is a side view diagram illustrating an alternative embodiment. The optical signal conduit **824** is formed on the substrate **826**. The optical signal conduit **824** has a grating coupler **822**. In such an embodiment, a laser or other light source may be provided remotely, and may be directed into the grating coupler **822** where incoming light **820** it is transmitted into the optical conduit **824**.

FIGS. **9**A-**9**F are cross sectional views of a lower wafer **900** at various stages of manufacture according to one or more embodiments. Initially, FIG. **9**A illustrates a lower wafer **900** in an early stage of manufacture. An optical signal conduit **902** may be disposed on a substrate **906**, with the substrate **906** being a material such as, but not limited to, glass, silicon (Si), gallium arsenide (GaAs), fiberglass, metal, or the like. Additionally, the substrate **906** may contain circuitry such as CMOS devices; interconnect lines; sensors; electrodes; photodetectors; doped regions, or the like, such as photosensor arrays **520**, **620**; ILD **530**, **630**; and bottom electrodes **540**, **640**. In one embodiment, the optical signal conduit **902** may be patterned to disperse light, or to provide separate conduit sections. An optical signal conduit **902** may, for example, be a dielectric material such as silicon nitride (Si3N4), silicon oxynitride (SiON), hafnium dioxide (HfO2), tantalum pentoxide (Ta2O5), or the like. A typical optical signal conduit **902** thickness may be between about 500 angstroms and about 6000 angstroms. In one embodiment, a dry etching technique may be employed to pattern the optical signal conduit **902**, and may provide better optical conduit critical dimension control than wet etching. Additionally, some embodiments may have an optical signal conduit **902** with a smooth outer surface, resulting in more efficient transmission of an optical signal.

FIG. **9**B illustrates a cross-sectional view of a lower wafer **900** after forming a sacrificial layer **912**. In one embodiment, a sacrificial layer **912** may be a hard or non-polymer material such as germanium (Ge), silicon (Si), titanium tungsten alloy (TiW), aluminum (Al), or the like, and may advantageously be deposited over the substrate **906** and optical signal conduit **902** by plasma deposition, chemical vapor deposition, physical vapor deposition, or the like. In one embodiment, the sacrificial layer **912** may have a thickness between about 2000 angstroms and about 6000 angstroms.

FIG. **9**C illustrates a cross-sectional view of a lower wafer **900** after patterning the sacrificial layer **912**. The sacrificial layer **912** may be patterned or removed from regions outside of the future packaging covered area **922** via lithography, or any other suitable process, leaving sacrificial layer **912** material only in the packaging covered area **922**. Removal of the sacrificial layer **912** may be accomplished by an etchant appropriate for the particular sacrificial layer **912** material, including, but not limited to, hydrogen peroxide (H2O2), phosphoric acid (H3PO4), potassium hydroxide (KOH), tetramethylammonium hydroxide (TMAH), ethylenediamine pyrocatechol (EDP), xenon diflouride (XeF2), and the like.

FIG. **9**D illustrates a cross sectional view of a lower wafer **900** after forming a bonding layer. A bonding layer **934** may be deposited over the patterned sacrificial layer **912** and optical signal conduit **902**. In one embodiment, the bonding layer **934** may be applied so that it lies in the bonding area **932** to cover the optical signal conduit **902** and provide a pad for bonding a cap wall over the signal conduit **902**. The bonding layer **934** may be, in some embodiments, an oxide such as silicon dioxide or the like, and may be deposited via, for example, a chemical vapor deposition process, a plasma enhanced deposition process, or any other suitable process. Alternatively, the bonding layer **934** may be a nitride, a metal layer, a polysilicon layer, or the like, and the bonding layer material may be selected depending on the optical signal conduit **902** properties. The sacrificial layer **912** may shield the optical signal conduit **902** from an overlying bonding layer **934**, in the region where the bonding layer **934** will later be removed.

In one embodiment of the present principles, it may be advantageous to have a hard sacrificial layer **912** instead of a sacrificial photoresist (PR) under the bonding layer **934** because polymer residues could interfere with the surface chemistry of the lower wafer **900**. Additionally, the planarization of bonding layer **934** that would be deposited on a sacrificial photoresist layer may be problematic because the oxide is on a soft material: the stress and pressure from planarization may cause a polymer-type photoresist to deform and the bonding layer to fail during the planarization. However, a biocompatible photoresist may be used, and the chemistry of such a biocompatible photoresist may be determined by the test material intended for a capped area, which will be discussed later. In such an instance, a biocompatible photoresist chemistry will preferably be selected to not interfere with the testing procedure and chemistry of any target molecule.

The bonding layer **934** may be deposited at a thickness over the substrate **906** surface between about 4 micrometers (40,000 angstroms) and 0.5 micrometers (5,000 angstroms) and may be subsequently planarized, using for example, a chemical mechanical polish, down to a thickness between about 2 micrometers (20,000 angstroms) and about 0.4 micrometers (4,000 angstroms). The bonding layer **934** may provide a planarized surface capable of accepting a range of bonding technologies while permitting an optical signal conduit **902** thickness up to about 600 nanometers (6,000 angstroms). Thus, one useful embodiment may be where the optical signal conduit is between about 200 nanometers (2,000 angstroms) and about 600 nanometers (6,000 angstroms) thick, and the bonding layer covers the optical signal conduit **902** while having a planarized bonding surface.

FIG. **9**E illustrates a cross sectional view of a lower wafer **900** after patterning the bonding layer **934**. The bonding layer **934** may be patterned or formed into cap bonding pads **904** by etching to remove the bonding layer **934** material in order to define or form a packaging covered area **922**, with bonding layer **934** material remaining in the bonding areas **932** as a target for bonding cap walls **904**. In one particularly useful embodiment, the bonding layer **934** may be etched using a dry etch technique, such as plasma etching or ionic sputtering. Alternatively, and depending on the bonding layer **934** material, a wet etch, or any other type of etching, may be advantageously employed to pattern the bonding layer **934**. In one embodiment, the bonding layer **934** may be planarized prior to patterning, which may avoid damage or contamination of portions of the substrate or optical signal conduit that may be unintentionally exposed from topography-induced insufficient mask or photoresist coverage during patterning. Additionally, planarizing the bonding layer **934** prior to patterning reduces or prevents damage or destruction by planarization of regions whose bonding layer has been patterned away.

FIG. **9**F illustrates a cross-sectional view of a lower wafer **900** after the sacrificial layer **912** is removed, exposing the optical signal conduit **902**. Removal of the sacrificial layer **912** may be performed by, for example, a wet or vapor etch in a similar manner as described above for the sacrificial layer **912** patterning. Thus, the optical signal conduit **902** is exposed in the packaging covered area **922**.

FIG. **10** is a cross-sectional diagram of an upper wafer **1000** that may be used in a bio-entity manipulation and processing system. The upper wafer **1000** includes an upper substrate **1010**. In the depicted embodiment, an upper substrate **1010** is a glass or silicon wafer, and does not need to be transparent. However, in other embodiments, upper substrate **1010** may be a substrate formed from another suitable elementary semiconductor, such as diamond or germanium; a suitable compound semiconductor, such as silicon carbide, indium arsenide, or indium phosphide; or a suitable alloy semiconductor, such as silicon germanium carbide, gallium arsenic phosphide, or gallium indium phosphide. Over upper substrate **1010** is a top electrode **1020**. In the depicted embodiment, top electrode **1020** is an indium tin oxide (ITO) layer. However, in other embodiments, top electrode **1020** may be an aluminum layer, aluminum-copper alloy layer, or another suitable electrode layer.

A dielectric layer **1030** is deposited over the top electrode **1020**. In this example, the dielectric layer **1020** is a high-k dielectric layer that has been deposited by an ALD process before being annealed. Additionally, on top of the dielectric layer **1030** is a hydrophobic coating **1040**. In the depicted embodiment, the hydrophobic coating **1040** is made from PTFE, but in other embodiments the hydrophobic coating **1040** is made from a self-assembling monolayer.

FIGS. **11**A and **11**B illustrate a bonding of a lower wafer **900** and an upper wafer **1000** for use in a bio-entity manipulation and processing system **1100**. FIG. **11**A illustrates an embodiment of a bio-entity manipulation and processing system **1100** with cap bond pads **904** disposed under the cap wall **1104** and covering the optical signal conduit **902** outside of the capped area **1108**. FIG. **11**B illustrates an embodiment of a bio-entity manipulation and processing system **1100** with cap bond pads **904** disposed in the area under the cap wall **1104** but exposing the exterior portions of the optical signal conduit **902**. The cap bond pad **904** and sacrificial material **912** remaining outside the capped area **1108** may be removed to expose the exterior portion of the optical signal conduit **902** during the steps illustrated in FIGS. **9**B through **9**F. Alternatively, the exterior portion of the optical signal conduit **902** may be exposed in a separate step, for example, after the cap **1102** is applied to the cap bond pads **904**.

The cap wall **1104** may be bonded to the cap bonding pads **904** using an adhesive such as an epoxy, via fusion bonding, or any other suitable technique. In one useful embodiment, for example, fusion bonding with low temperature (<300° C.) anneal may be suitable where the cap bonding pad **904** material is an oxide. The upper wafer **1000** may be bonded to the cap wall **1104** to form a cap **1102** and define the capped area **1108**. The capped area **1108** may be provided with a gaseous environment or fluidic material prior to bonding the upper wafer **1000**, or via a sealable opening after the cap **1102** is bonded. The cap **1102** will preferably be configured to remain water- or liquid-tight in an embodiment where the capped area maintains a fluidic material. Likewise where the capped area **1108** maintains a gaseous material, the cap **1102**, including the cap's structures and bonded seams will be gas-impermeable.

Separation of the bonding material and cap walls **1104** from the optical signal conduit **902** by the cap bonding pads **904** permits a planar bonding surface, since the bonding layer **934** and cap bonding pads **904** are laid over the signal conduit **902** and substrate **906** and then planarized. As the bonding pad **904** is planarized, the bonding pad **904** may be used to compensate for topography created by the optical signal conduit **902** as well as by the substrate **906**. Skilled artisans will recognize that in order to maintain a suitable planar surface, the cap bonding pads **904** will be at least as thick as the optical signal conduit **902** is high so that the cap bonding pads **904** lie on top of the optical signal conduit **902**. In particularly useful embodiments, the optical signal conduit **902** will be less than about 600 nanometers, with the planarized cap bonding pads **904** being thicker than the optical signal conduit **902**.

FIG. **12** is a cross-sectional diagram of an integrated microfluidic bio-entity manipulation and processing system **1200** that integrates the lower wafer **500** of FIG. **5** and the upper wafer **1000** of FIG. **10**. Thus FIG. **12** includes the substrate **510**, with the fluidic control circuitry, the photosensor control circuitry, and the logic circuitry thereon, in addition to the photosensor array **520** therein. An ILD **530** surrounds those features, and the integrated lower wafer **500** includes bottom electrodes **540** deposited thereon with an overlying dielectric layer **550**. In certain regions where the dielectric layer **550** does not cover the electrodes, the dielectric layer **550** can function as an optical signal conduit, as described with respect to FIGS. **7** through **9**F. On top of the dielectric layer **550** is a hydrophobic coating **560** that serves as the bottom of a microfluidic channel **1210**.

The microfluidic bio-entity manipulation and processing system **1200** also includes upper wafer **1000**, which includes upper substrate **1010**, which in this embodiment is a silicon substrate. Over upper substrate **1010** are a top electrode **1020**, a dielectric layer **1030**, and a hydrophobic coating **1040**. The lower wafer **500** and upper wafer **1000** are combined using the methods described with respect to FIGS. **11**A and **11**B so that the surface treated area **570** is aligned with the photosensor array **520** and so that the hydrophobic coatings **560** and **1040** are brought close together, without contacting, to form the microfluidic channel **1210**. In the depicted embodiment the surface treated area **570** is formed on hydrophobic coating **560**, which may improve performance by bringing the surface treated area **570** closer to photosensor array **520**. The presence of hydrophobic coating **560** below surface treated area **570**, however, is not required.

In operation, a droplet **1202** is brought into contact with the surface treated area **570** containing receptors using the actions depicted in FIG. **3**, such as the lateral movement **300**A. The droplet **1202** includes a tagged bio-entity sample, such as a specific DNA base mixed in the droplet such as the exemplary adenine reagent droplet **408**B from FIG. **4**. When the droplet **1202** contacts the receptors at the surface treated area **570**, chemical reactions may remove the tag from the bio-entity samples in the droplet. The removal of the tag may enhance or intensify a photonic emission. In some embodiments, the attachment rather than the removal of the tag may enhance or intensify a photonic emission. The emission is sensed in the photosensor array **520**. This signal is captured by the photosensor control circuitry, and transmitted to the logic circuitry for signal processing. Depending on the frequency or color of the photonic emission, a specific base pair may be detected. In embodiments, in which antibodies in the droplet **1202** are being tested, the emission may indicate the presence of the particular antibody in the bio-entity sample in droplet **1202**. After the droplet **1202** has been processed in this manner, it may be moved out of the microfluidic channel **1210**, and may be moved out of the microfluidic grid **400**.

A method **1300** for manipulating and processing bio-entity samples with an integrated semiconductor device will now be described with respect to FIG. **13**. The method begins at step **1302** when a bio-entity sample droplet is obtained from a first reservoir. The first reservoir is coupled to a microfluidic grid. The method **1300** continues to step **1304** when the bio-entity sample droplet is transported from the microfluidic grid into a microfluidic channel using an electrowetting effect. In the microfluidic channel, the bio-entity sample droplet contacts the receptors on the surface treatment in the microfluidic channel. A biochemical reaction is triggered upon contact between the bio-entity sample droplet and the receptors on the surface treatment. At step **1306**, a photonic signal that is produced by the interaction of the bio-entity sample droplet and the receptors on the surface treatment is detected by a photosensor array that is formed on the lower or first substrate.

To better illustrate the method **1300** in operation, reference will be made to the integrated microfluidic bio-entity manipulation and processing system **1200** of FIG. **12** and some other figures discussed above such as FIG. **3** and FIG. **4**. The method may also be explained with reference to other embodiments of integrated microfluidic bio-entity manipulation and processing systems disclosed herein. Thus, reference to FIG. **12** is made by way of non-limiting example. A reservoir **410**A of FIG. **4** may include a larger volume of a bio-entity sample. By using the action depicted as droplet formation **300**D of FIG. **3**, a bio-entity sample droplet **1202** is formed from the larger volume and introduced into the microfluidic grid **400** of FIG. **4**. The bio-entity sample droplet **1202** is transported through microfluidic grid **400**, which includes a plurality of microfluidic channels, one of which is microfluidic channel **1210** of FIG. **12**. Microfluidic channel **1210** is located on top of a material stack deposited on lower substrate **510**, the top layer of which, hydrophobic coating **560**, supplies the bottom surface of the microfluidic channel **1210**. Transporting the bio-entity sample droplet **1202** through the microfluidic channel **1210** is accomplished by using the logic circuitry to control the fluidic control circuitry.

The bio-entity sample droplet **1202** is moved through the microfluidic grid **400** of FIG. **4** and the microfluidic channel **1210** of FIG. **12** by using the electrowetting effect. Bottom electrodes **540** are asserted in either ON or OFF states as indicated by FIG. **3**, in order to subject the biological droplet **1202** to controlled hydrophobic or hydrophilic surfaces according to the ON or OFF states of the bottom electrodes. By control of the bottom electrodes **540**, and in conjunction with a top electrode **1020**, the bio-entity sample droplet **1202** is guided into contact with the surface treated area **570**, which has had a surface treatment applied to it. Guiding the bio-entity sample droplet **1202** into contact with the surface treated area **570** is accomplished by having the logic circuitry exert control over the fluidic control circuitry.

Because of the surface treatment, receptors in the surface treated area **570** and the bio-entity sample droplet **1202** may undergo a biochemical reaction which intensifies or enhances the fluorescent light signal. This light is received by a photosensor array **520**. Photosensor **520** detects the light and a corresponding signal is sent to the logic circuitry for processing. The logic circuitry may interpret the signal by color or frequency to determine the biochemical reaction that occurred. The biochemical reaction may indicate that a specific base nucleotide was detected in a target DNA fragment, or that a particular antibody was present in the bio-entity sample droplet. After the bio-entity sample droplet **1202** has been processed, it may be removed from the microfluidic channel **1210**. In some embodiments a buffer droplet, such as buffer droplet **408**A of FIG. **4**, may be transported through the microfluidic channel **1210** in order to clean it.

Additionally, in some embodiments of the method, an adenine reagent droplet **408**B obtained from the adenine reagent tank **406**A in FIG. **4** is combined with the bio-entity sample droplet **1202**, using the droplet merge **300**C operation of FIG. **3**. The droplet merge **300**C operation may mix the bio-entity sample droplet **1202** and the adenine reagent droplet **408**B in the microfluidic grid **400**. The mixed bio-entity sample droplet **1202** may then be directed into contact with the surface treated area **570** in the microfluidic channel **1210**. In other embodiments, a reagent other than the adenine reagent droplet **408**B may be used to create a different mixed bio-entity sample droplet **1202**.

Advantages of the integrated microfluidic bio-entity manipulation and processing system are provided by the optical signal conduit on the substrate **510**. Light delivery to the analysis site via the evanescent wave is done through the optical signal conduit, thus making the need for a transparent substrate and transparent top electrode unnecessary for a bio-entity analysis scheme involving EWOD. This provides for greater flexibility in the materials used. Moreover, bio-entity analysis involving the optical signal conduit may avoid the need for color filters integrated above the photosensors because the EWOD method can restrict particular base pairs to be sequenced at the moment, avoiding the need for color differentiation. One of the broader embodiments is an integrated semiconductor device for manipulating and processing bio-entity samples. The device includes a lower substrate, at least one optical signal conduit disposed on the lower substrate, at least one cap bonding pad disposed on the lower substrate and over a portion of the optical signal conduit, a cap that includes an upper substrate and configured to form a capped area, and disposed on the at least one cap bonding pad, a microfluidic channel, a photosensor array coupled to sensor control circuitry, and logic circuitry coupled to the fluidic control circuitry and the sensor control circuitry. The at least one optical signal conduit extends from outside the capped area to inside the capped area. The first side of the microfluidic channel is formed on the lower substrate and a second side of the microfluidic channel is formed on the cap, the cap being coupled to the substrate so as to provide the microfluidic channel for a droplet containing a bio-entity sample and the microfluidic channel being coupled to fluidic control circuitry. The fluidic control circuitry, the sensor control circuitry, and the logic circuitry are formed on the lower substrate.

Another of the broader embodiments is an integrated semiconductor device for manipulating and processing genetic samples. The device includes a lower substrate, at least one optical signal conduit disposed on the lower substrate and configured to transmit light to a target molecule, at least one cap bonding pad disposed on the lower substrate and over a portion of the optical signal conduit, a cap comprising an upper substrate and configured to form a capped area, and disposed on the at least one cap bonding pad, a surface treated area with receptors disposed within the capped area and on the lower substrate and configured to interact with the target molecule, a microfluidic channel, and a photodetector disposed within the lower substrate and configured to detect a response from the target molecule. The at least one optical signal conduit extends from outside the capped area to inside the capped area. A bottom surface of the microfluidic channel is formed on the lower substrate and a top surface of the microfluidic channel is formed on the cap, the cap being coupled to the substrate so as to provide the microfluidic channel.

Yet another of the broader embodiments is a method for manipulating and processing bio-entity samples with an integrated semiconductor device. The method includes providing a bio-entity sample droplet from a first reservoir, the first reservoir coupled to a microfluidic grid, transporting the bio-entity sample droplet from the microfluidic grid into a microfluidic channel using an electrowetting effect, the bio-entity sample droplet contacting a surface treatment in the microfluidic channel, wherein one side of the microfluidic channel is provided on a lower substrate, transmitting light to the surface treatment through an optical signal conduit disposed on the lower substrate, and detecting a photonic signal with a photosensor array, the photonic signal being enhanced by an interaction of the bio-entity sample droplet and the surface treatment, the photosensor array being formed on the lower substrate.

The preceding disclosure is submitted by way of discussion and example. It does not exhaust the full scope and spirit of the disclosure and claims. Such variations and combinations as may be apparent to one of skill in the art are considered to be within the scope and spirit of this disclosure. For instance, throughout the disclosure, DNA sequencing is presented as an example, along with antibody identification. The scope and spirit of the disclosure extends well beyond the limited context of these examples. Thus, the full extent of the disclosure is limited only by the following claims.

What is claimed is:

1. A device comprising:

an optical signal conduit disposed on a first semiconductor substrate;

a surface treated structure disposed over the first semiconductor substrate, the surface treated structure in communication with the optical signal conduit to receive an optical signal from the optical signal conduit;

a first electrode disposed over the first semiconductor substrate;

a cap configured to form a capped area, the cap including a second electrode, wherein the optical signal conduit and the surface treated structure are disposed at least within the capped area; and

a fluidic channel, wherein a first side of the fluidic channel is formed on the first semiconductor substrate and a second side of the fluidic channel is formed on the cap, the cap being coupled to the first semiconductor substrate, and wherein movement of fluid through the fluidic channel is controlled by electric fields associated with the first and second electrodes.

2. The device of claim **1**, wherein the first electrode includes a plurality of first electrodes disposed over the first semiconductor substrate.

3. The device of claim **1**, further comprising:

a dielectric layer disposed on the first electrode; and

a hydrophobic coating layer disposed on the dielectric layer, wherein the hydrophobic coating layer defines at least a portion of the fluidic channel.

4. The device of claim **3**, wherein the hydrophobic coating layer includes a material selected from the group consisting of polytetrafluroethylene and a self assembled monolayer.

5. The device of claim **1**, further comprising a photosensor disposed on the first semiconductor substrate, the photosensor operable to detect an emission occurring on the surface treated structure.

6. The device of claim **1**, wherein the cap further includes:

a second semiconductor substrate;

a dielectric layer disposed on the second semiconductor substrate such that the second electrode is embedded in the dielectric layer; and

a hydrophobic coating layer disposed on the dielectric layer, wherein the hydrophobic coating layer defines at least a portion of the fluidic channel.

7. The device of claim **6**, wherein the second semiconductor substrate that is bonded to the first semiconductor substrate via bonding pad.

8. The device of claim **6**, wherein a portion of the optical signal conduit extends beyond the capped area between the first and second semiconductor substrates.

9. A device comprising:

an optical signal conduit disposed over a first semiconductor substrate;

a non-transparent cap structure disposed over the optical signal conduit and defining a capped area above the substrate;

a surface treated area with receptors disposed within the capped area and configured to receive an optical signal from the optical signal conduit;

a fluidic channel, wherein a bottom surface of the fluidic channel is formed over the first semiconductor substrate and a top surface of the fluidic channel is formed by the non-transparent cap structure;

a photodetector at least partially embedded within the first semiconductor substrate and configured to detect an emission occurring on the surface treated area; and

an anti-reflective coating layer disposed over the first semiconductor substrate such that the anti-reflective coating layer is positioned between the photodetector and the surface treated area.

10. The device of claim **9**, wherein the receptors of the surface treated area are configured to interact with a fluid disposed within the fluidic channel, and

wherein the receptors interactions with the fluid causes the emission, and

wherein the emission is a light signal.

11. The device of claim **10**, wherein the fluid includes a biological entity.

12. The device of claim **9**, further comprising a plurality of tanks each containing a different biological entity, and

wherein the fluidic channel is part of a microfluidic grid for transporting the biological entities from the plurality of tanks through the microfluidic grid.

13. The device of claim **9**, wherein the non-transparent cap structure includes a second semiconductor substrate.

14. The device of claim **9**, wherein a hydrophobic coating layer forms the bottom surface and the top surface of the fluidic channel.

15. The device of claim **9**, further comprising a dielectric layer disposed directly on the anti-reflective coating layer, wherein the surface treated area is disposed directly on the dielectric layer, and

wherein the anti-reflective coating layer is disposed directly on the first semiconductor substrate.

16. A method comprising:

moving a sample through a fluidic channel to a surface treatment area, wherein a first side of the fluidic channel is provided on a first semiconductor substrate; and

detecting a photonic signal by a photodetector, the photonic signal produced by an interaction of the sample and the surface treatment area, wherein the detecting of the photonic signal by the photodetector occurs without the photonic signal passing through a color filter.

17. The method of claim **16**, wherein the sample includes a material selected from the group consisting of DNA, RNA, a protein, a small molecule, a virus and a pathogen.

18. The method of claim **16**, further comprising directing radiation to the surface treatment area.

19. The method of claim **16**, wherein the moving of the sample through the fluidic channel to the surface treatment area occurs via an electrowetting effect.

20. The method of claim **16**, wherein a second side of the fluidic channel is provided on a second semiconductor substrate, the second side of the fluidic channel opposing the first side of the fluidic channel.

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